

# Critical Care Sedation

Angelo Raffaele De Gaudio  
Stefano Romagnoli  
*Editors*



Springer

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## Preface

In the last 20 years, victims of critical illness have become increasingly elderly and frequently subject to multiple organ dysfunction. Critical illness is currently defined by certain syndromes, such as sepsis or acute renal failure, or by physiological alterations, such as shock states or hypoxemia. It is hence often necessary to integrate the more traditional subspecialties of medicine into critical care practice. For these reasons, critical care demands continuous advances in technology, therapeutics, and monitoring to improve the prognosis of disease states that influence organ physiology, especially in elderly patients.

Attention to sedation and analgesia in intensive care units (ICUs) has evolved during the last years, and significant evidence of its influence on patient outcomes has emerged. In light of this, those privileged to take care of patients in the ICU have witnessed a dramatic evolution from former practices of deep sedation lasting for several days to a gentler approach that treats “light sedation” for cooperative patients as the indisputably preferable option. Patients’ brains are vulnerable organs in the context of the multiple organ dysfunction that commonly characterizes critically ill patients. Sedation causes both brief and long-lasting injury that may manifest delirium and cognitive impairment.

This book, with its precious contributions from authors selected from physicians and researchers who handle sedatives and analgesics in their daily clinical practice, provides readers with an overview of current knowledge and the most up-to-date literature. The contents are designed to cover a number of issues directly or indirectly related to analgo-sedation in the ICU. Drugs currently in use (e.g., benzodiazepines or propofol) and newer molecules or applications (e.g., dexmedetomidine, halogenates) are discussed in relation to different aspects of patient care, including stress response, pain management, instrumental and clinical monitoring, the immune system, and sleep quality and quantity. Issues such as pediatric population, neuromuscular blocking agents, regional anesthesia techniques, and delirium are also addressed. Our aim was to design a text that would both revise and update the basic subject matter while directing practitioners toward the confident use of a specific drug or technique.

As editors, we found the revision of individual manuscripts rewarding, and we believe that the subject matter displays a healthy balance between theoretical understanding and practical clinical implementation. We hope that readers will find the chapters both informative and useful for improving patient care in their everyday clinical practice.

Finally, we wish to thank the editorial team members of Springer International Publishing AG; Mr. Andrea Ridolfi, Clinical Medicine Books Editor; and Mr. Rakesh Kumar Jotheeswaran, Project Coordinator, for having provided support in editing all chapters of this book.

Florence, Italy  
January 2018

A. Raffaele De Gaudio, M.D.  
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Giovanni Zagli and Lorenzo Viola

## 1.1 Brief Historical Background

The first experience of intensive care of critical patients, as it is generally acknowledged today, is attributed to Dr. Børn Aage Ibsen, a Danish anesthetist [1], considered the founder of intensive care medicine. His initiative was thought to support patients who required constant ventilation and surveillance after the poliomyelitis epidemic in 1952–1953 in Copenhagen (Denmark). Even though the use of a positive pressure ventilation outside the operating theater was not new, Dr. Ibsen initiated the concept of “secure artificial ventilation,” which was, at the time, very innovative. The consequence of this new concept was the creation of a multidisciplinary centralized unit with the aim of treating respiratory failures.

With the evolution of technology and the increase of intensive care unit (ICU) indications, intensivists came to understand the lack of comfort and the pain (both related to the cause of disease and to the invasive procedures for vital signs monitoring) of a patient admitted in ICU. These observations led to start the sedation/analgesic treatment of patients to permit the adequate invasive treatment. However, during the last years, a higher sensitivity to the psychological aspect of critical illness has been posed, improving the correct choice of drugs, psychological intervention (both to patients and relatives), and post-ICU follow-up to understand the consequences of a critical illness in terms of quality of life.

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## 1.2 Receptors Involved in Intravenous Sedation and Analgesia

### 1.2.1 $\gamma$ -Aminobutyric Acid (GABA) Receptors

GABA is the main inhibitory transmitter in brain tissue and the main target of sedative/hypnotic drugs. Since the second half of the last century, GABAergic drugs (such as alphaxalone-alphadolone) were used as hypnotic agents [2]. There are two known GABA receptors: GABA<sub>A</sub> receptor, which is a ligand-gated ion channel, and GABA<sub>B</sub> receptors, which is a G-protein coupled.

GABA<sub>A</sub> receptor is part of the loop family of receptors that included serotine, nicotine, and glycine receptors [3]. The GABA<sub>A</sub> receptor is a receptor-chloride ion channel macromolecular complex made by a pentameric complex assembled by five subunits ( $\alpha$ ,  $\beta$ ,  $\gamma$ ) arranged in different combinations. The possibility to have GABA<sub>A</sub> receptors made by different combination of the  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits permits to observe heterogeneity in terms of ligand affinity and, as consequence, on clinical effects, which depends also from the anatomical distribution of different GABA<sub>A</sub> receptor subtypes. The most common combinations of  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits are, in order, the  $\alpha 1\beta 2\gamma 2$ ,  $\alpha 2\beta 3\gamma 2$ , and  $\alpha 3\beta 1\gamma 2$  and  $\alpha 3\beta 3\gamma 2$  pentamers. The pentameric structure is assembled as a circle in a circle creating the transmembrane channel for chloride ions.

GABA<sub>A</sub> receptors are mainly located postsynaptically and mediate postsynaptic inhibition, increasing chloride ion permeability and so hyperpolarizing the cell. GABA<sub>A</sub> receptors are also located in the inter-synaptic space; thus, its released GABA produces inhibition by acting both directly to the postsynaptic neuron and at close distance.

GABA<sub>B</sub> receptor is a G-protein-coupled receptor (Gi/Go), which inhibits voltage-gated  $\text{Ca}^{2+}$  channels (reducing transmitter release), opens potassium channels (reducing postsynaptic excitability), and inhibits cyclic AMP production [4]. GABA<sub>B</sub> is composed of two seven-transmembrane domain subunits (B1 and B2) held together by an interaction between their C-terminal tails. GABA<sub>B</sub> is activated through binding with GABA and the extracellular domain of the B1 subunits that activates the B2 subunit; the receptor occurs when GABA binds to the extracellular domain of the B1 subunit: the interaction produced an allosteric change in the B2 subunit which interacts with the Gi/Go protein. GABA<sub>B</sub> receptors are located in both pre- and postsynaptic neurons.

Agonists of GABA receptors have different site of action. So, GABA, benzodiazepine, barbiturates, chloral hydrate, zolpidem, propofol, and alcohol (also antagonist as flumazenil) link to the receptors in different binding domains; this means that overstimulation of the GABAergic system can be easily obtained by simultaneous administration of different drugs.

As mentioned above, GABA acts as inhibitory transmitter. More than 20% of neurons in the central nervous system are GABAergics: the extensive distribution of

its synapses and the fact that all neurons are inhibited by GABA receptor activation summarized the importance of this inhibitory system.

Despite its incontrovertible inhibitory activity, during early brain development and also in some limited part of adult brain, GABA shows an excitatory effect due to a higher intracellular chloride ion concentration: this might be explained by the paradoxical effect of propofol (see below) in inducing myoclonus.

### 1.2.2 Opioid Receptors

The extract of *Papaver somniferum* has been used for thousands of years with the intent to produce analgesia, sleep, and euphoria and, more lately, also to treat severe cases of diarrhea. After the discovery of morphine chemical structures, many semi-synthetic compounds have been synthesized with the aim to increase the beneficial effects of opium and to limit the side effects. The observation that an exogenous molecule can interact with endogenous receptors conducted the researchers to isolate the endogenous opioid molecules [5, 6].

Three major classes of opioid receptors ( $\mu$ ,  $\delta$ , and  $\kappa$ ) have been firstly identified with pharmacological and radioligand binding approaches. The opioid receptor family was improved after the discovery of a fourth opioid receptor (Opioid-Like receptor, ORL<sub>1</sub>) which showed a high degree of homology in amino acid sequence toward the  $\mu$ ,  $\delta$ , and  $\kappa$  opioid receptors, even if naloxone did not interact with ORL<sub>1</sub>. The receptor previously denominated as “ $\sigma$ ” is not actually considered an opioid receptor, but it is perhaps a part of NMDA receptor system. The presences of numerous receptor subtypes have been postulated based on pharmacologic criteria, despite no different genes were discovered, maybe because different subtypes derive from gene rearrangement from a common sequence.

All opioid receptors are Gi/Go protein-coupled receptors [7]. The G-protein is directly coupled to specific ion channel, rectifying membrane potential through the open of a potassium channel and decreasing intracellular calcium availability through the inhibition of the opening of voltage-gated calcium channels (especially the N type). The cumulative effect is an inhibition of postsynaptic neurons. The inhibition at presynaptic neurons has been demonstrated for many neurotransmitters, including glutamate, norepinephrine, acetylcholine, serotonin, and substance P. All opioid receptors also inhibit adenylyl cyclase causing MAP kinase (ERK) activation, of which interaction with nuclear sites seems to be important in response to prolonged receptor activation, including toxicological effects and drug addiction. Since the transduction mechanism of signal is the same for all receptor subtypes, the differences in anatomical distributions is the main reason for the different responses observed with selective agonists for each type of receptor.

Main pharmacological effects mediated by different receptors are summarized in the following table:

Receptor	$\mu$	$\delta$	$\kappa$	ORL <sub>1</sub>
Analgesia				
Supraspinal	+++	—	—	— <sup>a</sup>
Spinal	++	++	+	++
Peripheral	++	—	++	—
Pupil constriction	++	—	+	—
Sedation	++	—	++	—
Respiratory depression	+++	++	—	—
Decreased gastrointestinal motility	++	++	+	—
Addiction and physical dependence	+++	—	—	—
Euphoria	+++	—	—	—
Dysphoria and hallucinations	—	—	+++	—
Catatonias	—	—	—	++

<sup>a</sup>It has been demonstrated that stimulation of ORL<sub>1</sub> supraspinal receptors can reverse the analgesic effects of  $\mu$  receptor agonists

Analgesia, sedation, respiratory depressant, euphoria, and physical dependence are mainly mediated by the  $\mu$ -opioid receptors. Although the development of selective agonists could be clinically useful, it is still not clear what makes the difference between morphine and endogenous opioid in terms of receptor subtype affinity. Central effects (sedation, euphoria, respiratory depression) are mediated by the supraspinal  $\mu$ -subtype receptors, and the analgesic effect is mediated in the spinal cord. Moreover, the  $\mu$  receptor is associated with Transient Receptor Potential Vanilloid (TRPV) 1 (see below). The increase of knowledge in TRP receptor family, its role in nociception and neuroinflammation, and its strict relation with opioids and cannabinoids might open new strategies for pain relief [8]. Opioid receptors are localized also peripherally, e.g., into the intra-articular space.

An uncommon (and uncomfortable) effect of opioids administration is the truncal rigidity, which reduces thoracic compliance and thus interferes with ventilation. The first hypothesis was a paradox effect mediated by the spinal cord opioid receptor, but recently a supraspinal action has been proposed.

During ICU stay, anxiolytic and relaxant effect mediated by opioid receptor stimulation is usually welcome and, in some most of cases, necessary to prevent continuous uncomfortable treatments (i.e., noninvasive ventilation) or breakthrough pain due to procedures or nursing. Nevertheless, a prolonged stimulation of opioid receptor system induced tolerance and usually needs an increase in dosage administered. The mechanism of opioid tolerance is still poorly understood, but the actual opinion is that persistent activation of  $\mu$  receptors might upregulate cyclic adenosine monophosphate (cAMP) system, inducing both tolerance and physical dependence. Physical dependence is defined as a characteristic withdrawal or abstinence syndrome when a drug (in this case opioids, but the concept is general in pharmacology) is suddenly stopped without any de-escalation strategy. Clinical manifestation (adrenergic system activation, agitation, sometimes respiratory distress) can be confused with critical illness-related complications, so the management of opioid

delivery should be strictly monitored and planned. In addition to the development of tolerance, prolonged administration of opioids can produce hyperalgesia. This phenomenon has been attributed to spinal bradykinin and NMDA receptor activation.

The challenge of a rapid opioid de-escalation can be particularly important in postsurgical patients, in which constipation can easily occur; especially in abdominal surgery, prolonged opioid administration can delay the recovery of gastrointestinal function, with the risk of complication or, at least, a longer ICU length of stay.

### 1.2.3 Glutamic Acid Receptors

L-Glutamate is the principal excitatory transmitter in the central nervous system, as almost all neurons are excited by glutamate [9]. Glutamate system works through the activation of both ionotropic and metabotropic receptors. Among ionotropic receptors, three main subtypes for glutamate have been isolated: NMDA (*N*-methyl-D-aspartate receptor), AMPA ( $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid), and kainate, so called originally according to their specific agonists. All these three types of receptors have a tetrameric structure composed of different subunits: this results in the presence of different receptors, with a complex and heterogenic distribution both in the central nervous system and in peripheral nerve termination [10].

Among them, NMDA receptors have been studied more in detail than the other types. NMDA channels are highly permeable to calcium ions; thus, their activation is very effective in calcium ions entry. NMDA receptors can be activated by both glutamate and aspartate, but they are also modulated by other amino acid transmitters, such as glycine and L-serine; moreover, also magnesium ions act as modulator or blocker (depending on site concentration) to inhibit NMDA channels. These peculiar characteristics of NMDA receptor may offer many possibilities to develop different molecules with synergic activity.

The importance of ketamine as a potent, high-affinity, noncompetitive NMDA receptor antagonist has been rediscovered in the last decade. Ketamine administration permits to obtain the so-called conscious sedation, during which the patient has an ideal level of analgesia and sedation but can appear awake. Ketamine is used particularly in hemodynamic shock with normal cardiac function, due to its property to induce analgesia and sedation without impact of peripheral vascular resistance. Moreover, ketamine does not inhibit significantly the respiratory drive of the patient, becoming an important drug to use during uncomfortable procedures out of the operating room. The effects of NMDA receptor antagonist are thus particularly interesting in the view of the development of new intravenous agent for sedation and analgesia without significant cardiovascular effects.

Concerning metabotropic receptors, there are eight different metabotropic glutamate receptors known, all members of class G-protein-coupled receptors, and they are divided in three classes. The first class is in the postsynaptic terminal as the ionotropic receptors, and it has excitatory activity as well, whereas the second and the third classes are mainly located in the presynaptic terminal and exert inhibitory/modulatory activity.



### 1.2.4 The $\alpha 2$ Adrenergic Receptors

The  $\alpha 2$  receptors are G-protein-coupled receptors which inhibit adenylyl cyclase, decreasing cyclic AMP formation; decrease calcium ion intake; and promote potassium ion outflow, resulting in cell hyperpolarization [11]. These receptors exert a very powerful inhibition of adrenergic tone, as can be observed in terms of decrease in blood pressure when clonidine, an agonist, is administered.

Dexmedetomidine is an agonist of  $\alpha 2$  adrenergic receptors, as well as clonidine, but unlike it, its action is more pronounced in the inhibition of central adrenergic tone despite the peripheral effect on hemodynamics. In the last years, dexmedetomidine has been successfully used for conscious sedation in critically ill and mechanically ventilated patients. The possibility to use intravenous sedation to increase patient's comfort without altering the hemodynamic parameter is still a challenge in the ICU; in this context,  $\alpha 2$  adrenergic receptors can become a new target to obtain this result.

---

## 1.3 Critical Care Sedation Concept

The need of an adequate sedation during intensive care interventions started over 50 years ago, during the first experiences with mechanically ventilated awake patients [12–15]. After ICU discharge, a lot of reports of “post-traumatic stress disorder” alerted physicians to the need to sedate patients [16]. On the other hand, the problem is the depth of sedation; nowadays, we must be technical to regulate the level of sedation with respect to:

1. Level of invasive care
  2. Duration of length of stay in the ICU
  3. Presence of relative (the so-called open ICU)
  4. Pain level
  5. Hypotension
- 
1. Patients with respiratory failure can often be initially treated with noninvasive ventilation, which required a low level of sedation/anxiolytic drugs, to permit a correct interaction between the patient and the ventilator. Naturally, in case of severe respiratory failure, the endotracheal tube and the invasive ventilation would impose to increase the level of sedation. Nevertheless, during the length of stay in the ICU, drugs could be de-escalated and a daily period of washout can be planned, possibly in the presence of relatives. Limiting the curarization at the initial phase of severe ARDS (without adopting a routine muscle relaxation protocol just to improve the patient/ventilation interface) must be guaranteed.
  2. Limitation of sedation is strongly linked with a shorter length of stay in the ICU, due to the lower incidence of neuromyopathy of critically ill patients. However,

the problem is still the reason for ICU admission. A major trauma probably will have a prolonged length of stay and, obviously, the need of a consistent sedation and analgic therapy. The question remains to identify the correct timing to de-escalate drug administration encouraging different modality to alleviate patient's stay.

3. The presence of relatives has been widely identified as a crucial factor to improve critically ill patients' comfort, and consequentially, it permits the reduction of sedation drugs and delirium incidence.
4. Level of pain must be constantly monitored and not confused with an inadequate sedation. In fact, hypnosis (sedation) and analgesia can be obtained using a combination of different drugs. The incidental pain (e.g., during nursing) should be treated with extemporaneous therapy and not improving the infusion.

In this context, when the illness will require a prolonged length of stay, a neurophysiological monitoring of level of consciousness (such as entropy) should be guaranteed as a basic level of care.

5. Vasoplegia is a constant effect of sedation and opioid administration. In this context, it must be taken into consideration that most of the intensivists' interventions (vasoactive administration, fluid overload) might be avoided just limiting sedative drug administration.

Propofol (up to 5 mg/kg/h) and dexmedetomidine (up to 1.2 µg/kg/min) are the most used hypnotic drugs in the ICU, combined with opioid agonists (fentanyl, morphine, remifentanyl). The use of benzodiazepine should be limited to limit intracranial pressure (as well as barbiturate) in patients with head trauma, intracranial hemorrhages, or epilepsy.

Recently, a new concept of sedation is starting to be used. The new technology known as Mirus™ permits sedation with Sevoflurane in the ICU: preliminary results suggest that patients can be sedated with a less need of vasoactive agent if compared with propofol.

Despite all these considerations, a recent Cochrane review failed to demonstrate that daily sedation interruption was effective in reducing duration of mechanical ventilation, mortality, length of ICU or hospital stay, adverse event rates, drug consumption, or quality of life for critically ill adults receiving mechanical ventilation [17].

Waiting for stronger evidence, the international opinion is that the reduction of sedative administration is to favor switching to maximize human contact. In this context, the eCASH concept (early Comfort using Analgesia, minimal Sedatives, and maximal Humane care) recently proposed by Vincent and colleagues [18] is based on improving analgesia and reducing sedation, promotion of sleep, early mobilization strategies, and improved communication of patients with staff and relatives.

Sedation in critically ill patients remains a challenge. The most important thing is to separate the pain control from the need of hypnosis. Diffusion of neurological monitoring might be facilitated by intensivists in this goal.

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# The Stress Response of Critical Illness: Which Is the Role of Sedation?

## 2

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*“Today there is a greater and growing awareness of the need to understand the disturbed metabolism and homeostatic mechanisms which come into play when man is injured, whether by accident or surgery, and how these reactions may be assisted in relation to improving the patient’s condition.”*

*D. P. Cuthbertson, 1975*

## 2.1 Introduction

The term stress defines any form of trauma, surgery, and infection that elicits a large number of neural and hormonal responses, resulting in an alteration of homeostatic mechanisms of the patient, who responds with a series of typical reactions, directed mainly to survival and then to healing.

The stress response has been described for the first time in 1932 by Cuthbertson [1] and confirmed 40 years later by Moore [2]). These authors observed a biphasic metabolic response: the first phase (termed ebb) represents a response of 24 h directed toward an immediate survival with an activation of mechanisms able to transfer blood from peripheral to the central circulation (heart and central nervous system) and to conserve body salt and water. The second phase (termed flow) known as hypermetabolism lasts 6–7 days and is characterized by an increase in total body oxygen consumption and CO<sub>2</sub> production, associated to catabolism of

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**Table 2.1** The three phases of stress response

	Ebb phase	Flow phase	Third phase or “chronic”
Duration	24 h	6–7 days	Months
Objective	Immediate survival	Hypermetabolism, substrate availability	Hypometabolism, substrate sparing
Response	Centralization of circulation, maintaining body salt and water	Muscle catabolism, gluconeogenesis, and nitrogen wasting Hyperglycemia and insulin resistance	Hormonal peripheral resistance, catabolism, and nitrogen wasting

skeletal and visceral muscle, gluconeogenesis, and protein synthesis [3]. Recently, a third phase (termed chronic) that may last some months and identifies the post-stress period of critical illness has been described. This third period seems characterized by different adaptive changes: the plasma levels of both pituitary and peripheral hormones are reduced, while a peripheral resistance to the effects of growth hormone, insulin, thyroid hormone, and cortisol persists. These hormonal alterations profoundly and sequentially affect the energy, protein, and fat metabolism [4] (Table 2.1).

Current insights suggest that the response involves not only a neuroendocrine and metabolic component but also an inflammatory/immune mechanism. Furthermore, some data demonstrated that adipose tissue and gastrointestinal hormones play an important role in this response. The final common pathway implies an uncontrolled catabolism and the development of a resistance to anabolic mediators [3, 4]. Sedation represents an intervention able to influence the stress response in critically ill patient, but literature data on the effects of sedative and analgesic drugs are old and lacking [5]. The effects are essentially related to a decreased neurohumoral reaction, involving the sympathetic system, with an effect on the inflammatory mechanism [6]. In this chapter, we describe current insights regarding pathophysiology of the stress response to critical illness and evaluating how sedation may influence it.

## 2.2 Stress Response: The Activation

The activation of the response depends on different mechanisms involving the neuroendocrine and the immune systems, with the release of hormones and other substances that influence organ failure.

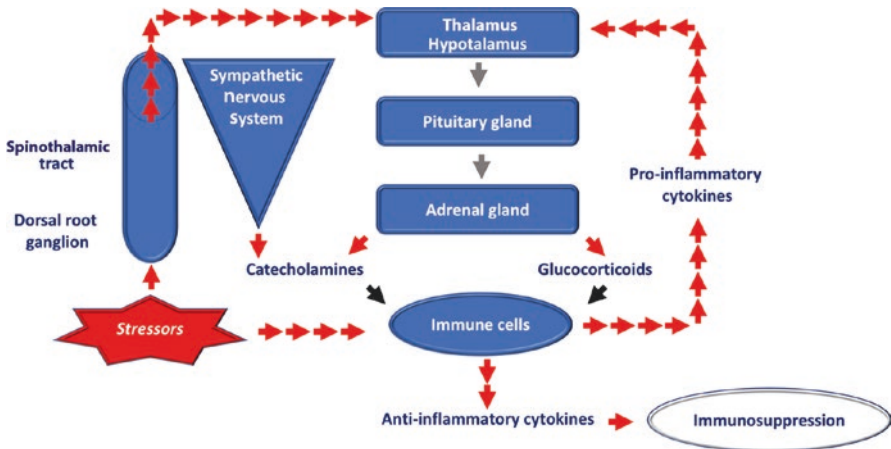
### 2.2.1 Neuroendocrine Mechanism

This component is triggered at hypothalamic level in the paraventricular nucleus and in the locus coeruleus and results in the activation of sympathetic nervous system (SNS) and hypothalamic–pituitary axis (HPA), secondary to different

stressors [7]: a peripheral tissue injury will activate afferent nerves; hypoxemia or hypercapnia will trigger chemoreceptors; and hypovolemia will activate baroreceptors [4]. Circulating concentrations of catecholamines are increased by an augmented SNS activity. The adrenal medulla releases norepinephrine and epinephrine into the bloodstream. At the same time, there is an increased secretion of the following pituitary hormones: adrenocorticotropin hormone (ACTH), growth hormone (GH), and vasopressin. Peripheral endocrine function produces an increase of glucocorticoids. In contrast, insulin secretion, if corrected for alterations in glucose concentration, is attenuated. Corticotropin-releasing hormone (CRH), released by the hypothalamus, stimulates the anterior pituitary release of ACTH into the bloodstream, and following ACTH stimulation, the adrenal gland produces cortisol: the so-called stress hormone [4]. The HPA is regulated by a negative feedback mechanism in which cortisol suppresses the release of both CRH and ACTH. Cortisol is a catabolic glucocorticoid hormone that mobilizes energy stores to prepare the body to react against stressors and stimulates gluconeogenesis in the liver, leading to raised blood glucose levels. Hyperglycemia reduces the rate of wound healing and is associated with an increase in infections and other comorbidities including ischemia, sepsis, and death. During and after surgery, the negative feedback mechanisms fail, and high levels of both ACTH and cortisol persist in the blood. In the presence of raised cortisol levels in a severe stress response, the rate of protein breakdown exceeds that of protein synthesis, resulting in the net catabolism of muscle proteins to provide substrates for gluconeogenesis [4]. Further substrates for gluconeogenesis are provided through the breakdown of fat. Triglycerides are catabolized into fatty acids and glycerol, a gluconeogenic substrate. Growth hormone-releasing hormone (GHRH) from the hypothalamus stimulates the anterior pituitary to release GH. Propagation of the GH-initiated signal occurs via the insulin-like growth factors which regulate growth. Signaling via these effectors regulates catabolism by increasing protein synthesis, reducing protein catabolism, and promoting lipolysis. Like cortisol, GH increases blood glucose levels by stimulating glycogenolysis. The hyperglycemic effect is also increased for the anti-insulin effects of GH [4]. Vasopressin is a major antidiuretic hormone released from the neurohypophysis, during stress, and it acts on arginine vasopressin receptors in the kidneys, leading to the insertion of aquaporins into the renal wall. Aquaporins allow the movement of water from the renal tubule back into the systemic circulation [4]. The total serum concentrations of thyroxine and triiodothyronine are globally decreased in critically ill patients, likely due to the reduction of thyrotropin. The altered feedback between thyrotropin-releasing hormone and thyrotropin is associated with lethargy, ileus, pleural and pericardial effusions, glucose intolerance and insulin resistance, hypertriglyceridemia, and decreasing muscular protein synthesis. These effects contribute to perpetuation of protein catabolism. The serum levels of triiodothyronine and thyroxine in high-risk patients are correlated with survival [5]. The benefits and risk of this body reaction are reported in Table 2.2.

**Table 2.2** Stress response: benefits and risk

Stress response	Positive effects	Negative effects
Increased heart rate (cardiac output)	Maintain mean arterial pressure and organ perfusion	Hypertension, myocardial ischemia, arrhythmias
Sodium and free water retention	Maintain intravascular volume	Congestive heart failure, pulmonary edema
Hyperglycemia	Substrate availability	Insulin resistance
Catabolism	Substrate availability	Malnutrition, nitrogen wasting
Endothelial activation	Increased platelet aggregation	Thrombosis



**Fig. 2.1** Stress response: relationship between stressors (trauma, surgery, infection), neuroendocrine activation, and immune/inflammatory mechanisms

**2.2.2 Immune Mechanisms/Inflammatory**

Pro-inflammatory cytokines such as tumor necrosis factor- $\alpha$ , interleukin-1 (IL-1), and interleukin-6 (IL-6), released from stress, activate immune cells, stimulate corticotropin-releasing hormone (CRH), and activate both the HPA and SNS [6]. These pro-inflammatory cytokines can impair some of the body’s physiological functions. For instance, tumor necrosis factor- $\alpha$ , IL-1, and IL-6 play significant roles in the metabolic changes associated with sepsis and septic shock. In addition to typical clinical signs of sepsis (fever, somnolence), these cytokines also induce weight loss, proteolysis, and lipolysis. In addition, these cytokines trigger anorexia at the hypothalamic level [4]. Catecholamines and glucocorticoids derived from the activation of HPA and SNS activate immune cells to produce also anti-inflammatory cytokines that suppress cell-mediated immune response, resulting in immunosuppression [6] (Fig. 2.1). The role of inflammation has been recognized in several trials in which has been demonstrated the role of intensive insulin therapy [8]. In experimental research, it was demonstrated that high glucose concentrations increase the production of pro-inflammatory mediators [9].

### **2.2.3 Adipokines and Gastrointestinal Hormone Mechanisms**

Adipokines (leptin, resistin, and adiponectin) are released from the fat tissue and are responsible for some metabolic alterations specially during sepsis and septic shock. The role played by gastrointestinal hormone is not very clear during stress: the circulating levels of ghrelin are reduced, while cholecystokinin is increased. These changes seem related to anorexia, expression of adaptation to stress [4, 11].

### **2.2.4 Uncontrolled Oxidative Stress Component**

Acute inflammation, ischemia–reperfusion, hypoxia, and hyperoxia are responsible for an imbalance between reactive oxygen species (ROS) generation and antioxidant levels by increasing the production of ROS or by consuming the stores of antioxidants or both. Furthermore, the oxidative stress will increase the inflammatory response, which produces more ROS as a vicious circle. The resulting imbalance between ROS and antioxidant protection mechanisms induces a damage on the protein, membrane lipids, carbohydrate, and DNA. Several studies suggest that the magnitude of the oxidative stress is related to the severity of the clinical condition [12].

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## **2.3 Stress Response: The Metabolic Consequences**

The endocrine response and the inflammatory mediators released induce some uncontrolled metabolic reactions expressed by the catabolism and the resistance to insulin. The magnitude of insulin resistance has been correlated with the severity of illness and considered as an adaptive mechanism designed to provide an adequate amount of glucose to the vital organs, unable to use other energy substrates in stress conditions [13]. This reaction is characterized by an increased central hepatic glucose production and a decreased insulin-mediated glucose uptake. The metabolic response is further enhanced, because of the presence of obesity and of nutritional support utilized [4]. These hormonal alterations modify the macronutrient utilization, while the energy needs are increased. The metabolic consequences to stress are part of the adaptive response to survive the acute phase of the illness characterized by a control of energy substrate utilization, partially regulated by substrate availability. Instead, the energy production is changed, and different substrates can be used with a variety of alterations, like increased energy expenditure, stress hyperglycemia, and loss of muscle mass [4, 8]. Inflammation could be responsible for changes of metabolic pathway response, and this concept has been demonstrated in several trials in which the magnitude of the inflammatory response was attenuated in patients who received intensive insulin therapy (IIT) and increased in patients who received no parenteral nutrition during the first week of critical illness [14, 15]. Experimental findings [16, 17] have consistently indicated



that high glucose concentrations increase the production or expression of pro-inflammatory mediators, adherence of leukocytes, alterations in endothelial integrity, and release of ROS by neutrophils, whereas insulin exerts the opposite effects [17]. High doses of insulin seem to reduce the levels of C-reactive protein in critically ill patients [8, 14]. These effects could be related to the anti-inflammatory effects of insulin or to an attenuation of the pro-inflammatory effects of hyperglycemia or both [19]. The available clinical data suggest that prevention of severe hyperglycemia may reduce cell damage; however, preventing hyperglycemia by using high doses of insulin, as required in cases of high intake of carbohydrates, can blunt the early inflammatory response. Resistance to the insulin provokes the muscle protein loss and function as a consequence of stress reaction. These metabolic alterations increase the rate of protein degradation more than the rate of protein synthesis, resulting in a negative muscle protein balance [8]. Kinetic studies have demonstrated an impairment in the amino acid transport systems and increased shunting of blood away from the muscles. The underlying mechanisms have been partially unraveled and include a relative resistance to insulin, amplified by physical inactivity [10]. Omega-3 fatty acids, growth hormone, testosterone, and beta-blockade could protect muscle strength and protein catabolism, preventing the muscular consequences of the stress response [8]. Monitoring the metabolic response is difficult because we have no specific markers but only indirect findings as incidence of secondary infections, muscle atrophy and weakness, respiratory insufficiency, and delayed wound healing [18, 19]. The high incidence of secondary complications indicates prolonged catabolism [12, 18, 20]. The clinical consequences include the following aspects: changes in resting energy consumption, the use of macronutrients as sources of energy, the stress hyperglycemia, and changes in body composition. The energy consumptions seem to be lower during the first ebb phase, with an increase during the flow phase and a slight decrease during the third chronic phase of critical illness [4, 21, 22], although this is extremely difficult to predict in critically ill patient, because energy consumption is influenced by fever, tachycardia, shivering, and agitation. At the same time, therapeutic interventions such as sedative agents, nonselective beta-blockers, and active cooling could influence the caloric changes [21, 22]. During stress, the alteration of macronutrient metabolism is involved at different levels: during the absorption, during the intracellular intermediate metabolism, and lastly during the oxidation of substrates. In critical illness, because of the increased requirements, the oxidative rate of carbohydrates, lipids, and proteins is regulated by the circulating hormones. In particular, the carbohydrate oxidation is higher than lipid and protein oxidation [8, 20]. The muscle may lose amino acids at the expense of the liver, to improve protein synthesis, reducing lipogenesis, with the only purpose of conserving lean body mass [4, 20]. As the turnover of glucose is increased, plasma concentrations of glucose will rise, resulting in the typical stress hyperglycemia [23]. Alteration of lactate metabolism is one of the consequences of the metabolic stress response. Lactate is a physiological intermediate energetic substrate produced from pyruvate reduction during glycolysis. The Cori cycle (conversion of lactate into glucose) confirms the ability of lactate to serve as a fuel expandable by organs in various

stress conditions. Most organs release and take up lactate. In stable conditions, the brain, muscles, and digestive tract produce lactate, whereas the liver is responsible for more than 70% of lactate clearance. Growing data support that these exchanges are favored during stress conditions and that lactate is a useful substrate used by organs and tissues during energetic crisis conditions and has been particularly demonstrated to fuel the heart and brain [4, 24, 25].

## 2.4    Effects of Sedative Agents on Stress Response in Critical Illness

The effects of analgesics and hypnotics on tissue metabolic demand of critically ill patient remain difficult to be adequately defined. In fact, these effects are reported only in some old and low-quality studies. The level of evidence is low and corresponding to “expert opinion” [5]. In addition, these agents might have potential physiologic repercussions on organ function and the healing process of critically ill patients, but these aspects have not received significant consideration so far. Most of the sedative agents are essentially able to decrease the neurohumoral mechanism of the response to stress, involving in the first place the sympathetic system, which could be effectively blocked (Table 2.3). Inappropriate sedation may impact on metabolic and immune function and contribute to morbidity and mortality. Inhibition or stimulation effects of sedative and analgesics may be significant, if these drugs are administered for a long period of time [5, 26, 27]. The reduction in tissue metabolic demand seems related to sedation in terms of decrease in muscular activity, reduction of work of breathing, and decrease in body temperature [5]. The effects of sedatives on cellular metabolism are limited because they can decrease only the functional component, especially at the level of the heart and brain. The control of the sympathetic activity may be useful in some critically ill patients, while in others the sympathetic blockade could be detrimental. Indeed, the sympathetic system plays an important role in the redistribution of blood flow according to local metabolic demand, especially when oxygen delivery is globally reduced. The complete blunting of the neurohumoral response to stress and therefore of the sympathetic system seems able to alter this physiological mechanism resulting in a decrease in tissue oxygen extraction capabilities. An imbalance between tissue oxygen demand and delivery could appear with the development of cellular hypoxia [5, 26]. The sedation of a critically ill patient requires careful evaluation of the level using

**Table 2.3**    The metabolic effects of sedatives in critically ill patient [5]

Direct effect	Indirect effect
Control on neuroendocrine activation	Reduction of oxygen consumption
Decrease in muscle activity	Reduction of oxygen cerebral consumption
Reduction in work of breathing	Reduction of hepatic and renal metabolism due to decreased blood flow
Decrease in body temperature	Reduction of metabolic consequences of stress response

appropriate scales. In patients in whom a reduction in metabolic demand is necessary, the effects of sedative agents on the oxygen consumption–oxygen delivery relationship must also be monitored [5, 26, 27]. While cardiac sympathetic stimulation may be advantageous in patients with good cardiac function, excess catecholamine levels can contribute to the development of problematic arrhythmias and myocardial ischemia in patients with underlying coronary diseases. In this clinical condition, catecholamine effects are able to extend infarct size, and the use of beta-blockers can be advantageous. Similarly, high levels of stress hormones can result in hyperglycemia, and this effect is paralleled by a marked increase in protein catabolism, which can contribute to the development of malnutrition. Combating the metabolic consequence is often difficult and requires the use of aggressive nutritional strategies. It is hypothesized that central nervous system activation with production of catecholamines and glucocorticoids, and systemic inflammation with cytokine production, could be responsible for the organ dysfunction [26, 28, 29]. *Opioids* offer optimal pain control acting mainly on  $\gamma$  and  $\kappa$  receptors, and through their analgesic effect, they attenuate the metabolic effects associated with stress [26, 31]. Morphine causes vasodilatation and has a sympatholytic action. Administering at high doses inhibits circulating concentrations of catecholamine, cortisol, and growth hormone. Fentanyl and hydromorphone are considered as possible alternatives. They are more potent and cause fewer hemodynamic changes. Remifentanyl, the ultrashort-acting opioid, is able to attenuate the hemodynamic response to painful stimuli, related to procedures in nursing and physiotherapy but can increase pain after the interruption of the administration [26–28]. It is well known that opioids have significant side effects on critically ill patient such as nausea and vomiting, itching, and ileus. Furthermore, there is an active debate regarding the role of opioids on the depression of immune response that might be undesirable in ICU patients [26–28]. This topic will be discussed in a dedicated chapter of this book. *Benzodiazepines* (BDZ) were the most commonly used medications for sedation in the history of ICU. The effects of these drugs are characterized by anxiolysis, hypnosis, anticonvulsive activity, amnesia, and skeletal muscle relaxation. Midazolam is, at the moment, the BDZ of first choice, because of its rapid onset of action with limited side effects on cardiorespiratory depression. The use of these drugs together with opioids seems to maintain low endogenous levels of epinephrine and norepinephrine. It is necessary to remember that the use of flumazenil, the specific antagonist of BDZ, in patients receiving continuous sedation with midazolam is associated with an increase of plasmatic levels of epinephrine and norepinephrine [26–28]. Propofol is cleared faster than midazolam and is rapidly eliminated from the central compartment; therefore a more rapid natural endocrine/metabolic restoration has been supposed. The administration of this anesthetic drug has been associated with arterial hypotension, due to a peripheral vasodilatation, and the fall in cardiac output can also be the result of myocardial depression. Supplementary intravenous administration of fluids and vasopressors is necessary to correct the hemodynamic impairment, while continuous infusion has been shown to have no significant effects on cortisol plasmatic level [26–30]. *Propofol* infusion syndrome demonstrates a correlation between the administration of this drug and metabolic alterations. This

syndrome concerns a rare and often fatal complication characterized by cardiac failure, rhabdomyolysis, severe metabolic acidosis, and renal failure, and reported in patients receiving catecholamine or steroids and undergoing long-term sedation with propofol. *Dexmedetomidine* is a selective  $\alpha$ -2 agonist that acts on locus coeruleus and has both analgesic and anxiolytic properties. The administration of this drug seems accompanied by potential inhibitory effects on cortisol synthesis and elevated plasmatic concentrations of growth hormone, whereas C-peptide (related to endogenous secretion of insulin) is decreased. This effect could be related to catecholamine suppression [26, 31]. Since surgical procedures are associated with complex and variable stress responses, characterized by neurohumoral, immunologic, and metabolic alterations, studies specifically focusing on the neuroendocrine and metabolic responses during *volatile anesthetics* administration are not available. However, it has been observed that sevoflurane and desflurane impact on the neuroendocrine stress response during and after surgery in a different modality with a higher efficacy of sevoflurane in reducing the release of catecholamine in comparison with desflurane. In addition, desflurane seems to better control the elevation of ACTH and cortisol than sevoflurane [32]. Differently, in a prospective randomized clinical study, on women requiring laparoscopic pelvic surgery (low stress laparoscopic surgery), isoflurane plus fentanyl or sevoflurane plus fentanyl resulted in similar catecholamine levels but significant decrease of ACTH, cortisol, and growth hormone levels but enhanced prolactin levels in the first group. The study concluded that more favorable metabolic and immune response changes were associated with sevoflurane administration in comparison with isoflurane [33]. In conclusion, although the effects of inhalation anesthesia on the modulation of neurohormonal response to surgical trauma remain unclear, clinical evidence is accumulating that these anesthetics are able to influence the stress response, by stimulating, inhibiting, or modulating complex pathophysiological pathways which induce neurohormonal and immunologic alterations [34].

## Conclusions

The consequences of stress response in critical illness still continue to be discussed and are not well understood. Outcome data examining benefits and adverse effects are lacking, due to significant inhomogeneity in patient presentation, a lack of opportunity to intervene prior to the stressor, and the variable presence of confounding co-stressors (e.g., hypoxia or sepsis). Some of the clinical manifestations that represent the result of the response to stress could be attenuated by sedatives and analgesics, but a careful monitoring of the level of sedation is necessary. The complete blunting of the neurohumoral response to stress and therefore of the sympathetic system seems able to alter this physiological mechanism and result in a decrease in tissue oxygen extraction capability. In summary, the stress determines negative consequences that sedatives may control maintaining a balance between beneficial effects (management of stress) and detrimental effects (hemodynamic alterations, immunosuppression, delirium, etc.). Further studies in this area may provide important new insights into the body responses and add to our understanding of the clinical importance of the stress.

Moreover, specific clinical trials could answer to different questions as: Which is the optimal sedative regimen? Which is the best combination and/or association? Which is the role of sedation with inhalation anesthetics, especially on immune response?

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## 3.1 Introduction

Staying in intensive care units (ICUs) has been described as a dramatic human experience, and pain is a major contributor. Indeed, pain is commonly reported by patients admitted to ICUs [1]. Surgery, invasive devices or baseline conditions may all contribute to its onset or exacerbation. Among many factors, tracheal intubation, mechanical ventilation and nursing are reported as major sources of pain or discomfort in those patients [2].

Pain is not only unacceptable as a human experience but is also a major contributor to morbidity of ICU patients, both in terms of increased incidence of delirium and requirements of sedative/analgesics with their side effects. Thus, prevention and treatment of pain are morally mandated and part of a good medical practice in ICUs [3–5].

An appropriate pain control allows to reduce the sympathetic burden of the patient, reducing oxygen consumption and insulin resistance and possibly contributing to immune modulation [6]. In critically ill patients, control of pain is a prerequisite of agitation control, i.e. an agitated patient should be assessed for the need of analgesia prior to be sedated. This approach, the so-called analgo-sedation, has proven efficacious in reducing the use of sedatives in ICU, thus contributing to a reduced rate of delirium, shorter length of stay and better outcomes [7]. Finally, incidence of long-term pain, which can occur in ICU survivors, can be reduced by an optimal pain control during the ICU stay [5].

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## 3.2 Physiology

The “physical feeling of pain” originates in tissues and travels to the brain via a simple neural network:

- The first sensitive neuron (“pseudo-unipolar”) senses the local release of mediators of tissue damage such as bradykinin, substance P, prostaglandins, potassium and others through its dendritic ends and activates the second sensitive neuron in the medulla (spinal-thalamic neuron).
- The second sensitive neuron transmits the painful sensation to the thalamus (spinal-thalamic tract).
- The thalamic-cortical tract transmits the painful feeling to the cortex, where pain becomes consciously perceived and a response is eventually elaborated.

When the thalamus is activated, a modulating, descending response is also built that starts in the periaqueductal grey matter and acts at spinal levels, inhibiting the activation of spinal-thalamic tract by the pseudo-unipolar neuron [2]. This mandates a “multimodal approach” to analgesia, i.e. many different analgesic techniques or drugs can be simultaneously employed to block pain at different levels (see Sect. 3.3). As an example, opioids or paracetamol blocks the transmitting of pain from periphery; nonsteroidal anti-inflammatory drugs (NSAIDs) reduce local release of mediators; local anaesthetics inhibit the action potential travelling along pain tracts, peripherally or centrally [8, 9]. Clinically, multimodal analgesia has been suggested as a tool to implement the synergistic effect of analgesics reducing their doses and side effects [10].

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## 3.3 General Principles

### 3.3.1 Assessment of Pain in ICU

Being a subjective feeling, pain can be very difficult to assess in ICUs, particularly in semiconscious or intubated patients, whose communication skills can be variably impaired. Thus, routine assessment of pain and need for analgesics is recommended by many guidelines [11–13].

In patients who can speak and/or communicate, visual analogue scales (VASs) may be used, which include continuous or discrete numeric scales. VASs have the advantage of being easy to apply and not expensive and are globally validated and accepted as a tool to assess pain and pain control [14].

In semiconscious or intubated patients, pain is suspected when facial expressions like grimacing or signs of sympathetic activation such as tachycardia, hypertension or tachypnoea are seen [15]. The Behavioral Pain Scale and the Critical Care Pain Observation Tool (CPOT) are tools that include behaviours and sympathetic activation as part of a global evaluation of discomfort in ICU patients [16–18].



All these tools can be used not only to assess pain but also to drive therapy. As for sedation, pain control should be patient-centred and goal-directed. Even though the goal of analgesia should always be the complete abatement of pain, side effects of analgesics must be taken into account too (e.g. respiratory depression or ileus); thus, a minimum level of pain, which could be acceptable for the single patient, needs sometimes to be targeted and tolerated to avoid these effects. Pain assessment tools may help to attain and maintain this level.

### 3.3.2 Multimodal Analgesia

Most of the evidence about analgesia in ICUs involve surgical patients admitted postoperatively. The general principles of acute pain management in these patients applies to ICU patients too. As stated above, a combination of techniques, drugs and routes of administration is generally recommended to optimise analgesia and reduce the side effects of single agents, particularly opioids. Opioid-driven respiratory depression and ileus can contribute to a substantially increased ICU-LOS; tolerance and opioid-induced hyperalgesia can ensue, making pain control difficult to attain [19]. However theoretically advantageous, multimodal analgesia is considered a standard of care only for postoperative, ICU patients, while many medical patients can be safely managed with single, low-dose analgesics [13, 20].

Even though intravenous infusion is generally preferred in ICU patients, oral administration can be considered in those whose gastrointestinal tract is normal, i.e. when oral or enteral feeding is well tolerated [21]. Sublingual administration can be considered as well, particularly for postoperative patients needing morphine or sufentanil [22]. Subcutaneous or intramuscular administration should be avoided because of potentially inadequate absorption due to hypoperfusion or tissue oedema; additional pain and risk of hematoma/local infection counter-indicate this route.

Intravenous administration can be done in boluses or as continuous infusions. Boluses can be administered “as needed”, possibly using an assessment tool like the VAS as a target; or they can be given as a “pre-emptive” analgesia, i.e. analgesics are given just before the painful stimulation. This last approach is preferred in otherwise “pain-free” patients who will face a single painful stimulation, like the insertion of a chest drain [23].

If patients can cooperate, patient-controlled analgesia (PCA) is the gold standard of pain control. In this case, the patient is instructed to self-administer a bolus of analgesic when she or he feels is necessary to achieve pain control. A safe interval lock-time can be chosen to avoid overdosing; if needed, a background, continuous infusion can be added to optimise pain control. In postoperative patients, PCA has been shown to be the most effective and safe modality of analgesic administration [23].

In a multimodal approach, these modalities of infusion (boluses as needed, pre-emptive boluses or PCA) can be applied also to epidural infusion. Epidural PCA (PCEA) is the gold standard of pain control in thoracic and major abdominal surgery. In this setting, PCEA may contribute to a reduced rate of respiratory complications and better outcome [23].

**Table 3.1** Equipotential doses of opioid agents

Analgesic	Strength (relative)	Parenteral dose (mg)
Codeine	0.1	100
Tramadol	0.1	50–100
Piritramide	0.7	7.5–15
Morphine	1	5–10
Oxycodone	1.5–2	4.5–6
Buprenorphine	40–50	0.15–0.3
Alfentanil	10–50	0.5–1
Fentanyl	70–100	0.05–0.1
Sufentanil	500	0.025

### 3.3.2.1 Opioids

Intravenous opioids (Table 3.1) are the treatment of choice for most ICU patients with acute pain, due to their potency and safety profile. Opioids can be used in association to sedatives as part of a strategy to manage agitation in ICU [24].

If a deep level of sedation is needed, as in mechanically ventilated, postoperative patients, *sedo-analgesia* is chosen, i.e. a continuous co-administration of sedative and analgesic agents. If a light level of sedation is indicated, *analgo-sedation* is the preferred technique, i.e. an analgesic driven continuous infusion during which sedatives are given only as low doses of short-acting agents in case of “breakthrough” agitation.

The pharmacologic bases of this approach are linked to the pleiotropic effects of opioids on several receptors. All opioids (agonists, antagonists, and mixed agonist–antagonists) act primarily through the binding to the  $\mu$ -opioid receptor. Other receptors include  $\kappa$ -opioid receptor and  $\delta$ -opioid receptor [19]. All three receptors ( $\mu$ ,  $\delta$ ,  $\kappa$ ) mediate analgesia but have differing side effects. M-receptors mediate respiratory depression, sedation, euphoria, nausea, urinary retention, biliary spasm, and constipation. K-receptors mediate dysphoric, sedative and diuretic effects.  $\Delta$ -receptors mediate euphoria, respiratory depression and constipation [25].

Morphine is the most commonly used opioid both in and outside ICU [26, 27]. Equipotential doses of opioids are comparative in respect to morphine (Table 3.1). Onset of analgesia for i.v. administration is 5–10 min, with peak effect occurring in 1–2 h. Sublingual administration can be used in postoperative patients; there are some data suggesting that pre-emptive use can reduce postoperative opioid consumption. Morphine doses are titrated to the desired effect, and its efficacy monitored with a consistent pain assessment tool (see above). Morphine has an elimination half-life of 4–5 h. Hepatic conjugation leads to formation of glucuronide metabolites, whose renal elimination occurs in 24 h [28]. In ICU patients with reduced creatinine clearance (particularly below 30 mL/min), the morphine-6-glucuronide can accumulate and account for prolonged analgesia and side effects, particularly over-sedation and respiratory depression [29].

Fentanyl is a synthetic derivative of morphine. It is approximately 100 times more potent than morphine, exhibiting a faster onset due to higher lipid solubility and penetration into the blood–brain barrier [26, 30]. Side effects too are more pronounced, including sedation and respiratory depression. Fentanyl can be administered as pre-emptive/rescue boluses or as continuous i.v. infusion. However, its

potential for accumulation in fat tissues and muscles counter-indicates prolonged infusions, which are linked to prolonged sedation [31]. In case of renal dysfunction, the use of single boluses of fentanyl may be preferred to morphine continuous infusion [32].

Remifentanyl is an ultrashort-acting fentanyl derivative with fast onset/offset of action (<3 to 5–10 min). Analgesic potency of remifentanyl is similar to that of fentanyl. Its favourable pharmacokinetics is linked to its organ-free, extensive inactivation by circulating esterases; this makes remifentanyl a good option in cases of renal or hepatic dysfunctions [10]. Due to its potency and sedative effects, remifentanyl may be used as the main drug during ICU analgo-sedation (see above): a continuous infusion of remifentanyl can be supplemented as needed with single boluses of short-acting sedatives, i.e. propofol or midazolam. This strategy has been suggested to reduce duration of mechanical ventilation and ICU-LOS, even though evidence is not definitive in this sense [24, 33]. Major drawbacks of its potency include a major degree of respiratory depression at relatively low doses (>0.05 µg/kg/min) and fast onset of opioid-induced hyperalgesia; its cost may be of concern too [34, 35]. Finally, since the drug is licenced only for a short lasting continuous infusion, longer infusions may be considered off-label.

Sufentanil is a synthetic, potent opioid with highly selective binding to µ-opioid receptors. Analgesia induced by sufentanil has a potency seven- to tenfold higher than fentanyl and 500- to 1000-fold higher than morphine (per oral dose). The high lipophilicity of sufentanil allows it to be administered sublingually and achieve a rapid onset of analgesic effect [22, 36]. Data on sublingual use of sufentanil in ICU patients are scarce, and its use cannot be routinely recommended in all patients.

Tramadol is a centrally acting opioid-like drug and acts by binding to the µ-opiate receptor as a pure agonist; it inhibits adrenaline and serotonin reuptake. It is used to treat moderate to severe pain [37]. The most common adverse effect is typical to other opioids and includes nausea, vomiting, dizziness, drowsiness, dry mouth and headache. However, tramadol produces less respiratory and cardiovascular depression than morphine, and euphoria and constipation are also less common [38].

### Non-analgesic Effects of Opioids

- Opioids exert sedative properties that are proportional to their analgesic potency. In mechanically ventilated ICU patients, this effect may be advantageous and may be part of a “sedative-sparing” regimen (analgo-sedation). However, in spontaneously breathing patients who are being weaned from ICU supports, opioid-driven sedation may be undesired and problematic; as such, light sedation with shorter-acting sedatives such as midazolam and dexmedetomidine may be preferable [39].
- Respiratory depression is proportional to analgesic potency; chest wall rigidity may be of concern with fentanyl and remifentanyl. Respiratory depression is usually seen as an undesired side effect, particularly in ICU patients who are spontaneously breathing [40, 41]. However, in selected cases, a carefully titrated

infusion of an opioid may reduce respiratory workload and oxygen consumption and increase compliance to non-invasive mechanical ventilation (NIV). The elderly, the obese and those patients with hepatic/renal dysfunction are particularly prone to undesired and prolonged respiratory depression. In these cases, naloxone can be used as the antagonist to reverse opioid-induced respiratory depression. This reversal may be associated with sudden reappearance of pain, tachycardia, hypertension and pulmonary oedema. Attention must be paid to these effects in cardiopathic patients.

- Delirium, which can be due to uncontrolled pain, may be related to appropriately prescribed opioids as well. In general, as per all undesired effects of drugs, opioids should be discontinued and an alternative strategy for pain control should be adopted [24]. In case of persistent delirium, other organic causes need to be ruled out and a specific treatment is indicated.
- Opioid-driven hypotension may be linked to histamine release, particularly by morphine; or it can be the direct vasodilatory effect of these drugs [19, 42]. As such, in hemodynamically unstable patients, single boluses should be administered slowly, and a cautious infusion of the less potent morphine could be preferred. Bradycardia may ensue, particularly with remifentanyl and sufentanyl, and it may be of concern for patients with rate-dependant cardiac output; however, in tachycardic and normo-/hypertensive patients, bradycardia can reduce myocardial oxygen consumption and left ventricular wall stress.
- Gastrointestinal effects: nausea, vomiting and ileus are commonly observed during opioid administration and are linked to activation of brain's chemoreceptor trigger zone or intestinal receptors [40]. Ondansetron, alizapride or metoclopramide may help reduce the rate of opioid-associated nausea and vomiting. Ileus better responds to cessation of administration [43]. If this is not possible, i.v. inrastigmine can be administered, if not contraindicated. Alternative strategies for pain control should be considered in these cases.
- Tolerance, i.e. a reduced clinical effect of opioids over the time, ensues typically during prolonged or chronic administration; with more potent agents like remifentanyl, it can ensue even after very short infusions. Mechanism of tolerance includes lower density of receptors on cell surface and receptor accommodation. Thus, to overcome it, it is advisable to bridge to other, non-opioids agents to control pain. However, an abrupt discontinuation may be linked to symptoms of withdrawal, which include abrupt breakthrough of pain, tachycardia/hypertension, profuse sweating and malaise; delirium may ensue as well. Clonidine or dexmedetomidine are typically used to control those symptoms. In complicated cases and in case of chronic opioid abuse and/or methadone treatment, a clinical toxicologist should be consulted.

Opioids can paradoxically induce hyperalgesia, through a sensitisation to painful stimuli [44]. This is more commonly observed with remifentanyl infusion. The exact mechanism is not well understood, even though the combination of extreme potency and ultrashort duration can play a role. Timely shifting from remifentanyl to morphine infusion is widely advised to minimise the risk of exacerbation of acute pain.

### 3.3.2.2 Non-opioid Analgesics

Non-opioid analgesic drugs can be employed as main therapy for pain control or associated with opioids as part of a multimodal strategy (see above). In this case, synergic effects of those agents allow a spare of opioids, reducing their doses and side effects. Due to their heterogeneous pharmacology, they can be employed in many different clinical settings. They are not devoid of potentially severe side effects, particularly cumbersome in ICU patients. Patients with renal dysfunction, gastrointestinal bleeding, recent surgical bleeding, platelet abnormality, cirrhosis or asthma are at risk of complication with nonsteroidal anti-inflammatory drugs (NSAIDs) [45]. Thus, their use must be carefully weighed against opioid side effects. Non-opioid analgesia may be used in ICU patients with mild to moderate acute pain, to reduce doses of opioids. Temperature and pain control can be achieved with paracetamol. Procedural analgesia can be performed with ketamine. All patients that develop tolerance or hyperalgesia with opioids need to be bridged to a non-opioid pain control strategy which may include NSAIDs use and clonidine/dexmedetomidine. In ICU patients with neuropathic pain, gabapentin or pregabalin can be used with or without concomitant use of opioids. For difficult cases of ICU patients chronically taking analgesics for pain syndromes, a pain medicine specialist should be consulted.

Parenteral paracetamol is an analgesic and antipyretic agent used in ICU patients to treat fever and/or mild pain. After surgery, paracetamol decreases the total needed dose of morphine [46, 47]. The individual response to analgesic effects of paracetamol is variable, with some patients being completely insensitive to its analgesic effects. In sensitive patients, pre-emptive paracetamol associated with a tramadol rescue dose may be a good strategy to control mild to moderate postoperative pain. Hypotension is a well-described side effect, particularly with parenteral administration; however, evidence is that paracetamol-driven hypotension is transitory and rarely needs pharmacologic intervention [48–50]. Of note, hemodynamic unstable patients or those with progressive or severe hepatic dysfunction should be spared paracetamol infusion. Renal dysfunction, on the contrary, does not counter-indicate its use.

NSAIDs are inhibitors of cyclooxygenase (COX), an enzyme of the arachidonic metabolic pathway which facilitates the release of pain mediators like prostaglandins, prostacyclins and thromboxane. NSAIDs, particularly ketorolac and ibuprofen, may be used as adjuncts in multimodal pain control strategies to spare opioid dosing [51, 52]. As stated above, renal and gastrointestinal side effects can be cumbersome in ICU patients, limiting their use to the stable, postoperative patient without renal, hepatic or platelet dysfunction [45]. When not counter-indicated, a single bolus of NSAIDs can be used as a rescue to treat mild to moderate breakthrough pain. The use of selective COX-2 inhibitors is discouraged to avoid potentially severe myocardial effects.

Ketamine provides dissociative anaesthesia and analgesia by blocking *N*-methyl-D-aspartate (NMDA) receptors and binding to  $\sigma$ -receptors for opioids. It is employed as a substitute or adjunct for opioid therapy in selected patients, particularly those with opioid tolerance or hyperalgesia [53–55]. Its use is associated with hallucination, and premedication with diazepam or midazolam is advisable [56].

Lidocaine is an amide local anaesthetic that has analgesic and anti-inflammatory properties. By blocking sodium channels, G protein-coupled receptors and NMDA receptors, lidocaine has multiple mechanisms of modulating pain. Intravenous lidocaine in abdominal surgery was associated with lower pain scores and opioid usage, faster return of bowel function and shorter length of stay as compared with controls. At blood levels  $>5$  mg/mL, serious toxic side effects are noted on the central nervous system, including focal and grand mal seizures, psychosis and rarely respiratory arrest. It is therefore crucial to check lidocaine levels on any patient in whom a lidocaine infusion is going to be administered and titrated to a level  $<5$  mg/mL [65]. In addition, in patients with peripheral neuropathic pain syndromes such as allodynia and hyperalgesia, a transdermal application of 5% lidocaine has proven to be effective at alleviating pain [66]. A lidocaine infusion in the intensive care setting has been shown to be effective as an adjunct to an opioid analgesic in the postoperative setting for the first 24 h [67]. Although many studies have validated the effectiveness of lidocaine in the perioperative setting with bowel surgery, further study is necessary in order to validate prolonged lidocaine infusion as a safe and effective analgesic in the intensive care setting.

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### 3.4 Adjuncts and Complementary Agents

Other drugs can be used as adjuvant analgesic therapy in the ICU: antidepressant, anticonvulsant agents and neuroleptics. Antidepressants are commonly used for various chronic pain conditions and are classified according to chemical structure and/or mechanism of action. The most common classes of antidepressants include tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors [57]. Antidepressants show efficacy in the treatment of chronic pain; multiple positive trials suggest the therapeutic potential of antidepressants for treatment of acute, or prevention of chronic, postoperative pain, which needed to be replicated [58].

Dexmedetomidine and clonidine are selective  $\alpha_2$ -central agonists with sympatholytic, sedative, analgesic and anti-shivering effects. They can be used to provide light sedation and analgesia to ICU patients. Their analgesic effect is mild, and they need to be associated as adjuncts to other, more potent analgesics. They are devoid of respiratory depressant effects, and thus they are particularly useful to manage pain and agitation in ICU patients on NIV, such as those with acute exacerbations of chronic obstructive pulmonary disease (COPD). In those patients,  $\alpha_2$ -central agonists have the advantage to control tachycardia and hypotension without inducing bronchospasm. Occasionally, they can be used to manage withdrawal from opioids or other drugs [59, 60].

Gabapentin and pregabalin are analogues of the gamma-aminobutyric acid (GABA) that can be used to treat neuropathic pain in the general and ICU population. They act inhibiting neurotransmission at the synaptic level of pain neurons [61]. Common dose-related adverse effects include somnolence and confusion. These agents may be used as adjuncts as part of a multimodal pain control strategy,

particularly in ICU patients already taking them at home [62, 63]. Gabapentin and pregabalin are available as oral medications; in ICU patients on mechanical ventilation, they can be administered via a nasogastric tube.

### 3.4.1 Regional Anaesthesia

In ICU patients, regional anaesthesia is most commonly performed through neuraxial blocks and peripheral blocks (e.g. transversus abdominis planus, TAP, or intercostal block).

Advantages of regional analgesia in ICU include [64–66]:

- A reduced need for i.v. analgesics, mostly opioids
- A faster weaning from mechanical ventilation
- A faster recovery of bowel function

Neuraxial analgesia is commonly used to treat pain in postoperative ICU patients since many high-risk patients who are managed with a programme of enhanced recovery after surgery (ERAS) will be postoperatively admitted in ICUs [67]. Other than retaining the general advantages of regional analgesia, neuraxial blockade may reduce the risk for thromboembolism and cardiorespiratory complications [64–66]. However, in ICU patients, the cardiocirculatory effects of neuraxial analgesia may be cumbersome and noradrenaline is often needed; weaning from noradrenaline may take time, thus increasing ICU-LOS. A proper, goal-directed strategy for fluid supplementation must be implemented in high-risk patients who undergo neuraxial blockade. In septic patients these techniques are better avoided for both the sepsis-related cardiocirculatory dysfunction and coagulopathy [67, 68].

The TAP block has been proposed to reduce opioid consumption in patients following abdominal surgery [69]; in ICU, the TAP block may be used in patients whose hemodynamic status counter-indicates neuraxial blocks. A TAP catheter may be left in place to provide a continuous infusion of local anaesthetics. However, pelvic and visceral pain is not covered by TAP and i.v. supplemental analgesia is often needed [70].

### 3.4.2 Non-pharmacologic Interventions

Physical therapy can help in increasing functional mobility and muscle strength, including respiratory muscles' strength and resistance [71]. Epidural analgesia, early mobilisation and early oral feeding are all part of the ERAS programs which aim at improving the outcome after abdominal surgery [72, 73]. Their role in ICU patients is more difficult to ascertain. Transcutaneous electrical nerve stimulation, relaxation techniques, massage therapy and music therapy may contribute to pain control in some patients [74].



## Conclusions

- Pain is common among ICU patients and can be due to either surgery, underlying conditions and ICU procedures.
- Routine assessment and management of pain are integral part of ICU good practice. The use of VAS or behavioural scales is recommended.
- In agitated patients, the need for analgesia needs to be ruled out prior of administration of sedatives.
- Medical ICU patients can be safely generally managed with a low dose, single agent infusion, such as morphine.
- Surgical ICU patients are better managed with multimodal analgesia, including PCEA, TAP block, oral or sublingual opioids and/or continuous infusion of morphine or more potent opioids.
- FANS,  $\alpha_2$ -agonists or complementary drugs such as antidepressants can be added as needed.

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# Common Practice and Guidelines for Sedation in Critically Ill Patients

## 4

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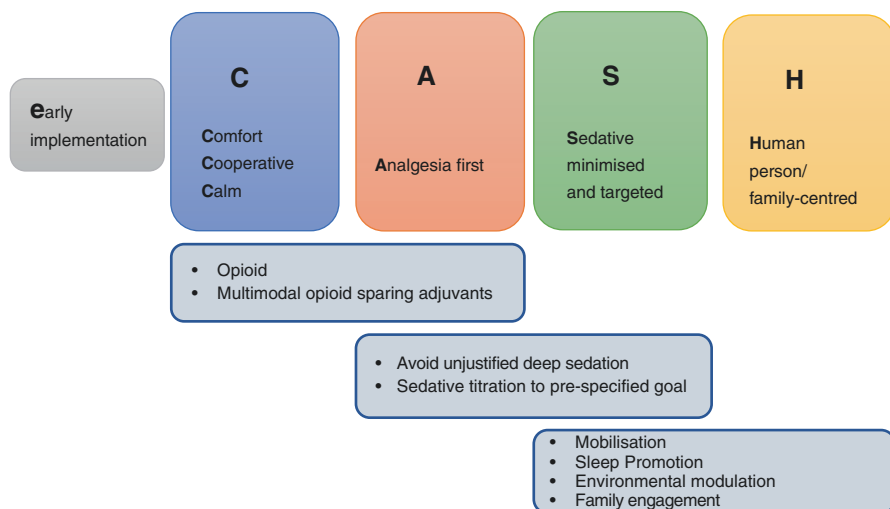
### 4.1 Introduction

The management of analgesia, sedation, and delirium (ASD) remains challenging in critically ill patients, particularly in specific populations and settings, for instance, elderly, children, and patients with shock, brain injury, or substance abuse. Long-term functional outcomes are closely related to ASD management. For instance, untreated pain and anxiety may lead to post-traumatic stress disorder and chronic pain after intensive care unit (ICU) discharge. Moreover, the occurrence of delirium is associated to high mortality rate, length of hospital stay, and long-term cognitive impairment [1–6].

Clinical practice guidelines (CPGLs) based on the best available evidence are essential for supporting the decision-making in daily practice, and several CPGLs on ASD have been published by international scientific societies of critical care medicine in the last decade. The quality of these CPGLs was recently assessed by Appraisal of Guidelines, Research, and Evaluation (AGREE) instrument [7]. Throughout the years, the quality of CPGLs significantly improved albeit methods for dissemination and implementation of the guidelines in clinical practice were rarely indicated also in the more recent CPGLs. The AGREE evaluation indicated that CPGLs by Pan-American and Iberica Federation of the Critical Care Medicine Societies [8], the American College of Critical Care Medicine (ACCM) [9], and the German Association of the Scientific Medical Societies (AWMF) [10] are high-quality documents and, thereby, should be recommended for use [7, 11, 12]. It is important also to note that the more recent CPGLs include specific recommendation for identification and management of delirium as well as for analgesia and sedation treatment in specific patient populations. For instance, the document by the AWMF

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**Fig. 4.1** The eCASH concept: Comfort using Analgesia, minimal Sedatives, and maximal Human care

[10] includes indications for pregnant, lactating, and moribund patients, and the guidelines by the Pan-American and Iberica Federation of the Critical Care Medicine Societies [8] provide indications also for patients with renal and liver failure. Besides CPGLs, an integrated and adaptable approach to improve patient care and clinical outcomes through analgesia and light sedation has been recently proposed by a panel of experts in ASD management. This approach aims to individualize the ASD management by achieving an early Comfort using Analgesia, minimal Sedatives, and maximal Human care (i.e., eCASH [13]) (Fig. 4.1).

Common criticisms that emerge from CPGL evaluation are related to the low level of evidence for the majority of the strong recommendations, particularly in analgesia and delirium management [7]. Given the paucity of high-level studies for many of the included items, questions on the reliability of these recommendations arise, whereas their effects remain uncertain and may differ considering different patients, context, and organization. Nevertheless, although many questions remain unanswered, we believe that CPGLs provide clear indication to better manage ASD in critically ill patients.

## 4.2 Sedation and Guidelines: Which Strategy?

Significant improvements in ICU-related organ support technology, such as advances in ventilator design, dialysis, and extracorporeal circuits, have strongly reduced the necessity of deep sedation in critically ill patients. Furthermore, numerous clinical experiences indicate that light levels of sedation in adult ICU patients are strictly associated to shorter duration of mechanical ventilation and shorter ICU length of stay [14–20], whereas deep sedation is linked with important side effects, such as increased

risk of pneumonia, venous thrombosis, ileus, hypotension, and a prolonged stay in the ICU. Thus, the most recent CPGLs strongly recommend that sedative medications have to be titrated to maintain a light rather than deep level of sedation, unless clinically contraindicated [8–10]. Moderate or deep sedation protocols remain applicable for specific settings including, for instance, severe respiratory failure with ventilator–patient asynchrony, prevention of awareness in patients receiving neuromuscular blocking agents, and severe brain injury with intracranial hypertension. However, the vast majority of ICU patients may benefit by light level of sedation that requires a multifaceted approach with attention to the choice of sedative agent(s) and to their pharmacodynamical and pharmacokinetic characteristics. These considerations led to a general retreat from benzodiazepines as first-line sedatives in the ICU and to move toward short-acting, easy-to-titrate agents such as propofol and dexmedetomidine. The high frequency of pain and discomfort as primary causes of agitation led to consider sedation protocols based mainly on analgesics (analgesia-first) [16, 19, 21, 22]. Although data seem to be encouraging, the role of this strategy should be further evaluated because of the low quality of the studies available and the uncertain results on the possible adverse effects related to the use of opiates. A trial including 140 ICU patients treated by morphine boluses and randomized to receive or not receive further sedatives demonstrated an increase of the incidence (from 7% to 20%) of agitated delirium in group treated only with opiates (i.e., no sedation groups) [19]. In addition, other potential adverse effects such as reduce gastric motility, pain recurrence, and withdrawal syndrome should be considered in an analgesia-first strategy.

Similarly to CPGL, eCASH experts also suggest to minimize the routine use of benzodiazepines by preferring agents that can be easily titrated to predefined targets depending on the patient's clinical needs. In addition, they suggest to eliminate sedatives at the earliest medically justifiable opportunity and support the use of an effective multimodal analgesia combined with early mobilization strategies, promotion of sleep, and communication of patients with staff and relatives.

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### 4.3 Sedation and Guidelines: Monitoring of Sedation Level

Numerous well-designed studies and clinical experiences demonstrated that an appropriate monitoring of analgesia and sedation allows a significant reduction of mechanical ventilation time, the ICU length of stay, and, thereby, the occurrence of nosocomial infectious complications, mainly ventilator-associated pneumonia (VAP) [11, 12, 23–28]. Some authors have also reported a decrease in mortality following the introduction of systematic monitoring of sedation levels [29]. In this light, personalized goal-directed protocols are better provided by the use of shared sedation scales. Those with broad acceptance include (among others) the Ramsay scale, the Sedation–Agitation Scale (SAS), the Motor Activity Assessment Scale (MAAS), the COMFORT scale for pediatric patients, and the Richmond Agitation–Sedation Scale (RASS). Of the available scales, the CPGLs recommend the use of the RASS and the SAS based on published literature and the psychometric properties of the scale [9, 10].



The RASS has been demonstrated to have excellent interrater reliability in a broad range of adult medical and surgical ICU patients and to have excellent validity when compared to a visual analogue scale and other sedation scales. This RASS takes less than 20 s to perform with minimal training and has been shown to be highly reliable among multiple types of healthcare providers. The RASS has an expanded set of scores (10-point scale) at pivotal levels of sedation that are determined by patients' response to verbal versus physical stimulation, which will help the clinician in titrating medications [30–32]. The SAS scale comprises seven categories, ranging from the absence of patient reactivity or responsiveness to dangerous agitation. It has been validated by several groups and is well accepted by the nursing personnel for documenting both the degree of sedation and the degree of agitation [33, 34].

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#### **4.4 Sedation and Guidelines: Alternative Adjunctive Strategies**

Nonpharmacological interventions of ASD are strongly supported by the CPGL that recommend to optimize patients' environment by implementing strategies to control light and noise and to decrease stimuli at night. This approach can significantly decrease the occurrence of agitation and delirium and, thus, the use of sedatives or antipsychotics with a true benefit for the critically ill patient. In fact, sleep disturbances are common in ICU patients and extremely disadvantageous. The lack of complete sleep cycles can contribute to the development of delirium and increased levels of physiologic stress. Given that, restoration of more normal sleep may become a therapeutic goal in the ICU. Therefore, application of a "sleep bundle," including maintaining regular sleep–awake rhythms; reducing light, noise, and care episodes during the nighttime; and using earplugs and music, may be helpful.

Beyond sleep bundle, CPGLs and eCASH document support the use of other adjunctive strategies for improving patient comfort in ICU. Early mental stimulation programs and physical activity may effectively reduce agitation, delirium, and ICU-acquired weakness. The risks of early mobilization seem to be smaller than anticipated, and the barriers to practical implementation, despite not passed over, may be conquerable [35, 36]. Additionally, a successful communication between patients, staff, and relatives may reduce the need for sedation and delirium occurrence. The use of inappropriate sedation strategies may cause brief and fragmented communications resulting in confusing or alarming messages to the patient. The use of light sedation strategies by the use of specific drugs reinforced by particular technical measures to enhance the quality of communication (e.g., specific tablet or PC apps for communication) can help patients to reestablish meaningful contacts with their surroundings facilitating reorientation. It must be noted that communication strategies can advantage patient's recovery and reorientation only if staff and relatives are responsive to the patient needs and able to respond in a comprehensible way. Moreover, special attention should be focus to the wishes of relatives with a review of the visiting hour policy as an integral part of this aspect of care and rehabilitation [13].



## 4.5 Sedation and Guidelines: Survey Results

Although the strong recommendations of the CPGLs and eCASH document on the appropriate level of sedation and its measurement, national and international surveys revealed low implementation of screening tools at the bedside, and remarkable variations still exist in the definition and assessment of optimal sedation. For instance, a tendency toward deep and oversedation has been reported by Jackson et al. in 2009 [37], while a survey on 1384 intensivists in North America [38] revealed that 60% of them assessed the occurrence of delirium but only 20% used a valid delirium assessment tool. In 2001, a large survey [39] reported that sedation practices are really heterogeneous in European countries. There is a significant difference ( $P < 0.01$ ) in the use of different sedatives: Midazolam was regularly used by 85% of respondents in Norway and only by 39% of respondents in Denmark; propofol was regularly used by 65% of Italian respondents and only by 3% of intensivists in Norway. As regards analgesics, morphine was used more commonly in the UK and Ireland, Sweden, Norway, Switzerland, Spain, Portugal, and the Netherlands, whereas fentanyl was preferred in France, Germany, and Italy and sufentanil in Belgium, Luxemburg, and Austria. Thereafter, other multicentered surveys sought out the degree of implementation within different countries. Mehta et al. [40] in 2006 published a cross-sectional mail survey among the Canadian practitioners to evaluate utilization of sedative, analgesic, and neuromuscular blocking agents, as well as the use of sedation scales and daily sedative interruption in mechanically ventilated adults. Only 29% of Canadian intensivists used a written protocol to administer sedative and analgesic drugs, while 40% routinely used a sedation scoring system (mainly the Ramsay scale) with a high variability in the frequency of assessment. Additionally, despite being recognized as frequent in ICU patient, only 3.7% used a delirium scoring scale. The sedation practice in the UK has been evaluated in 2008 [41], and their results were consistent with the aforementioned 2001 European survey, which showed that ICUs in the UK frequently use sedation scales: 88.1% of UK ICUs apply a sedation scoring tool, being the Ramsay sedation scale score the most widely used (66.5%). This also represents an important increase compared to a previous UK survey conducted in 2000, when only 67% of hospitals resulted using a sedation scoring system. Eighty percent of the responding hospitals have implemented an operating sedation protocol, and 43% reported the use of a written guideline. A similar scenario has been depicted in German ICUs [42] by a comparative cross-sectional multicenter survey aimed to evaluate changes in sedation management from 2002 to 2006. The use of sedation scores improved from 8% to 51%, as well as the use of sedation protocols moved from 21% to 46%. A 2009 multidisciplinary survey conducted in the United States also indicated an acceptable use of the strategies recommended by clinical guidelines and protocols [43]. A significant gap between the perceived importance of delirium in the ICU and the practices for monitoring and treatment was also found [38]. Delirium was recognized as a frequent and serious problem in critically ill patients by 92% of professionals, but only 16% used validated tools to identify it, and only 12% of respondents screened for delirium more times a day. A survey conducted among the members of the French ICU society in 2013 revealed that a number of barriers to the implementation of written procedures (e.g., insufficient education programs or understaffing) are still

present. Around 70% of responding intensivists assessed sedation and pain using validated scales, but only 38% of respondents regularly assess pain in noncommunicating patients [44]. The European survey published in 2013 [45] highlighted that 53% of the respondents use protocolized sedation and that formal sedation and assessment tools were more often used in Nordic countries, nations with a large number of nurses educated on the use of sedation scoring tools. As refers to delirium, 38% of nurses declared that delirium is mainly assessed by the Confusion Assessment Method for the ICU (CAM-ICU), whom 50% of them conducting this every shift.

Surveys offer a picture of actual practice and highlight the gap existing between clinical practice and current recommendations. Although the awareness is increasing that the use of protocolized algorithms and validated assessment tools for ASD management is a cost-effective strategy, the complete implementation of the most recent and evidence-based strategies is far from being fulfilled in daily routine. Many reasons can justify this gap. Tanios et al. [43] observed that the three most important perceived barriers limiting the bedside use of sedation protocols are lack of physician order, the nurse preferences to avoid the use of written protocols, and inclination of the caregivers to personalized sedation rather than to a schematic protocol. Moreover, lack of motivation, the poor competence in using specific tools, and personal beliefs, for instance, the perception that sedated patients do not experience pain, may also be relevant. Moreover, cultural differences emerged from European survey [45]: the Nordic context appears to be more suitable for the goal of light sedation with great attention to specific educational programs devoted to facilitate the implementation of ASD appropriate assessment and treatment in the daily practice.

#### **4.5.1 From Guidelines to Common Practice**

The practical application of CPGLs on ASD management, as for other CPGLs on different issues, is truly difficult. The worldwide variability in practice rules and in the resource availability makes implementation of evidence-based practices challenging [46, 47]. For instance, although nonpharmacological interventions are considered to be “low cost, easy to provide, and safe,” they are really complicated to implement and rarely applied in everyday practice because they require specific resources and education.

A successful strategy for CPGL implementation starts from the development of institutionally specific patient-centered protocols using an interdisciplinary team approach. In general, protocols facilitate the transfer of evidence-based “best practices” to the bedside, limit practice variation, and reduce treatment delays [18, 25, 27, 48]. Patient-centered model of care with effective team working has been associated with improvement in overall quality of care in ICU patients and cost reduction [11, 12, 25, 49]. Team working is considered the key factor for an appropriate management of the critically ill patients by several quality and safety organizations, including the Institute for the Healthcare Improvement. The shared time of rounding represents an opportunity for all the ICU team members to discuss how the patient is responding to the interventions recommended. The use of goal checklists, facilitated by the use of a standardized script that addresses many of CPGL suggestions, has also been shown to

significantly improve interprofessional communication, enhancing coordination of care and patient outcomes. Daily interprofessional rounding as well as the utilization of goal checklists, report scripts, and the ABCDE bundle (see below) can facilitate team working and, then, the transfer of CPGL recommendations in clinical practice.

It is important to notice that the management of ASD may conflict with other clinical goals [50] and be further complicated by the growing number of evidence-based treatments and clinical algorithms [3, 51]. Therefore, to further facilitate the bedside application of CPGLs, an integrated bundle approach has been proposed for the management of ASD [9, 52] (Fig. 4.2). Bundle, as a small set of evidence-based

Pain	Assess	Assess pain $\geq 4$ x/shift Preferred pain assessment tools: <ul style="list-style-type: none"><li>• Patients able to self-report: NRS (0-10)</li><li>• Patients unable to self-report: BPS (3-12) or CPOT (0-8)</li></ul>
	Treat	Within 30' then reassess: <ul style="list-style-type: none"><li>• Non pharmacologic treatment</li><li>• Pharmacologic treatment:<ul style="list-style-type: none"><li>- Non neuropathic: IV opioids +/- non opioids analgesic</li><li>- Neuropathic pain: gabapentin or carbamazepin + IV opioids</li><li>- S/p AAA repair, rib fractures: thoracic epidural</li></ul></li></ul>
	Prevent	<ul style="list-style-type: none"><li>• Pre-procedural analgesia and/or non pharmacological interventions</li><li>• Treat pain first, then sedate</li></ul>
Agitation	Assess	Sedation $\geq 4$ x/shift Preferred sedation assessment tools: RASS (-5 to +4) or SAS (1 to 7) NMB: suggest using brain function monitoring Depth of sedation, agitation defined as: <ul style="list-style-type: none"><li>• Agitated: RASS 1 to 4 / SAS 5 to 7</li><li>• Awake and calm: RASS 0 or SAS 4</li><li>• Lightly sedated: RASS -1 or SAS 3</li><li>• Deeply sedated: RASS -3 to -5 or SAS 1 to 2</li></ul>
	Treat	Targeted sedation or DSI: RASS= -2;0 or SAS= 3-4 <ul style="list-style-type: none"><li>• If under sedated (RASS&gt;0, SAS&gt;4): treat w/sedatives prn (non-benzodiazepines) preferred, unless ETOH or benzodiazepines withdrawal suspected</li><li>• If over sedated (RASS&lt;-2, SAS&gt;3): hold sedatives until target, then restart at 50% of previous dose</li></ul>
	Prevent	<ul style="list-style-type: none"><li>• Consider daily SBT, mobility and exercise</li><li>• EEG monitoring if:<ul style="list-style-type: none"><li>- At risk of seizure</li><li>- Burst suppression therapy is indicated for <math>\uparrow</math> ICP</li></ul></li></ul>
Delirium	Assess	Assess delirium Q shift Preferred delirium assessment tools: <ul style="list-style-type: none"><li>• CAM-ICU (+ OR-) • ICDSC (0 TO 8)</li></ul> Delirium present if: <ul style="list-style-type: none"><li>• CAM-ICU + • ICDSC <math>\geq 4</math></li></ul>
	Treat	<ul style="list-style-type: none"><li>• Treat pain as needed</li><li>• Reorient patients; familiarize surrounding;</li><li>• Pharmacologic treatment of delirium:<ul style="list-style-type: none"><li>- Avoid benzodiazepines unless ETOH or benzodiazepines withdrawal is suspected</li><li>- Avoid rivastigmine</li><li>- Avoid antipsychotics if <math>\uparrow</math> torsades de pointes</li></ul></li></ul>
	Prevent	<ul style="list-style-type: none"><li>• Identify delirium risk factors: dementia, HTN ETOH abuse, high severity illness, coma, benzodiazepines administration</li><li>• Avoid benzodiazepines in those at <math>\uparrow</math> risk of delirium</li><li>• Mobilize and exercise patients early</li><li>• Promote sleep</li><li>• Restart baseline psychiatric meds, if indicated</li></ul>

**Fig. 4.2** ABCDE bundle

practices, is frequently used in the ICU setting to address several serious conditions, such as the early management of sepsis and prevention of ventilator-associated pneumonia [53, 54]. As suggested in the study by Barr et al. [52], they can be pivotal for developing patient-centered protocols to ensure patients receive the best evidence-based treatments, especially considering the variability of manpower and resources of the ICUs. In addition, the use of bundled care approach is effective for improving the standardization and coordination of the ICU staff [55]. Specifically, the ASD bundle focuses on assessing, treating, and preventing pain, agitation, and delirium in an integrated manner and connects ASD management to other evidence-based ICU practices, for instance, spontaneous awakening trials (SATs), spontaneous breathing trials (SBTs), and ICU early mobilization programs. Although it does not propose a one-size-fits-all strategy, the treatment methods and goals are well defined and respect the recommendations of the CPGLs. The appropriate control and/or prevention of patient's pain is mandatory, and patient should be sedated only after an acceptable pain control. Sedation strategy should be defined considering the sedation goals for each patient and the pharmacologic profile of the agents, preferring non-benzodiazepine strategies and a light level of sedation with a positive interaction between patient and the ICU environment. Successful implementation of the ASD bundle requires an integrated and interdisciplinary team-based approach with engagement and activation of patients and relatives.

Although the true effects of ASD bundle implementation are not well defined, the application of individual elements, or the combination of two or more of them, appeared to significantly improve outcomes and reduce costs both in short- and long-term ICU patients. For instance, the Awakening and Breathing Coordination (ABC) trial [18] showed that patients managed with SAT and SBT experienced less time on mechanical ventilation and shorter ICU and hospital length of stay than patients managed only with SBT. Moreover, the duration of coma was shorter and survival rate at 1 year higher in patients managed with both SATs and SBTs. In addition, Schweickert et al. [56] demonstrated that the association of SAT and an early mobilization protocol can reduce the extent and time of delirium and increase the number of ventilator-free days.

Jablonski et al. [57] evaluated the efficacy of ASD bundle implementing them in a large academic surgical ICU. Data indicated a decreased use of continuous opioid infusions and improved time spent in light sedation with stable analgesia. Further, physical therapy activity sessions increased and ICU LOS and ventilator days trended lower.

Implementation of the ASD bundle may also result in considerable cost savings, as reported by an economic analysis [28] that evaluated the impact of a ASD bundle-based management protocol in a mixed medical–surgical ICU. In the protocol group, the ICU length of stay and the duration of mechanical ventilation were lower than in the pre-protocol group with a save of around 1000 USD for each hospitalization.

A recent systematic review [58] on the implementation strategies for the management of ASD and its impact on clinical outcome revealed high heterogeneity in terms of strategies used, and only few studies provided data on clinical outcomes.

Nevertheless, in the majority of the published experiences, the adherence to bundle application increases with a reduction in mortality and ICU length of stay in implementation programs that employed six or more strategies (including current evidence on pain, agitation, and delirium management) or when a strategy of early awakening, breathing, delirium screening, and early exercise (ABCDE bundle) was employed. Similarly, Collinsworth et al. [59] reviewed the effectiveness, implementation, and costs of multifaceted care approaches, including care bundles, for the prevention and mitigation of delirium in ICU patients. The majority of studies indicated that bundle approaches were associated with improved patient outcomes including reduced incidence and duration of delirium associated to a short length of ICU stay and decreased mortality.

Although numerous studies in the United States and Europe reported that the use of ASD protocols has remarkably improved patient outcomes, recent Australian studies did not confirm the results observed. These controversial findings may be related to differences in open or closed ICU models, nurse to patient ratios, nurses' education, and specialist medical training among countries.

In conclusion, multifaceted and multidisciplinary implementation programs involving also patients and relatives have been shown to effectively change adherence to ASD management. Implementation programs may enhance their effectiveness when not only healthcare professionals are targeted for behavioral change but also organizational changes are employed. Structured strategies including awakening, breathing, coordination, and early mobilization (ABCDE bundle) or integrated approach as eCASH seem to be associated with improved clinical outcomes and, therefore, are recommended for the transfer of CPGLs in clinical practice and to improve the pain, agitation, and delirium management in critically ill patients.

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# The Subjective and Objective Monitoring of Sedation

## 5

Carla Carozzi and Dario Caldiroli

### 5.1 Introduction

Proper and safe sedation requires close monitoring of the level of sedation in each patient. The target achieved must be frequently reevaluated to avoid over- or under-sedation as well as modified if the patient's clinical condition changes. Ideally the monitoring tool should be valid (validity), i.e., able to accurately diagnose sedation and discriminate between the various levels, and reliable (reliability), i.e., gives same result over time and among different examiners. And finally, it should be feasible (feasibility) that means easy to administer, remember, and communicate among all caregivers. As stated in the Pain, Agitation, and Delirium 2013 (PAD 2013) guidelines [1], these features allow not only the precise titration of sedation but also the timely correction of other causes of impaired consciousness such as anxiety, pain, or acute brain dysfunction (delirium or coma).

Monitoring tools may be subjective, i.e., based on sedation scales that are administered at regular intervals by caregivers, or objective through instruments that automatically diagnose the sedation level. The current monitoring has been subject to extensive revisions by various scientific societies and is constantly evolving. We currently have quite robust, validated tools, especially with regard to subjective clinical instruments.

PAD 2013 advise to increase the use of these tools since the clinical impact of proper monitoring is already widely documented. It reduces not only the use of sedatives but mainly improves ICU patient outcomes such as reduction of mechanical ventilation, ICU and hospital LOS, and decreased incidence of delirium and long-term cognitive dysfunction.

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## 5.2 Subjective Monitoring

Subjective monitoring of sedation means the clinical evaluation of an operator who observes and provides a stimulus to a patient following the procedural indications of a clinical sedation/agitation scale.

Each scale provides a score that quantifies the current degree of sedation or agitation of the patient. Several clinical scales have been created and validated over the years for ICU.

In the 1970s, the Ramsay Sedation Scale (RSS) (Table 5.1) has been developed [2]. Still widely used, it mainly explores the domain of sedation with only one level describing anxiety and agitation (score 1). However the goal of sedation in intensive care has profoundly changed over the last 30 years shifting from an unconscious and immobile patient to awake with light or no sedation and early mobility. Therefore, new sedation scales have been created to better intercept slightest differences in degrees of consciousness of an awake and contactable patient, with particular attention in assessing degrees of agitation as well as the cognition. The PAD 2013 experts ranked the most commonly used clinical scales according to the psychometric characteristics: validity, reliability, feasibility and relevance for practice, i.e. mainly the impact of implementation on patient outcomes. Moreover, they should have been developed in a rigorous multidisciplinary setting of significant patient populations (medical, surgical, and trauma ICU adult patients) and a robust number of participants.

The clinical scales are listed here from worst to best psychometric performances, according to PAD 2013 experts: Observer's Assessment of Alertness/Sedation Scale (OAA/S) [3], New Sheffield Sedation Scale [4], Sedation Intensive Care Score (SEDIC) [5], Motor Activity Assessment Scale (MAAS) [6], Adaptation to the Intensive Care Environment (ATICE) [7], Minnesota Sedation Assessment Tool (MSAT) [8], Vancouver Interaction and Calmness Scale (VICS) [9], Sedation-Agitation Scale (SAS) [10], and Richmond Agitation-Sedation Scale (RASS) [11]. The Sedation-Agitation Scale (SAS) and the Richmond Agitation-Sedation Scale (RASS) most fulfill all the criteria considered (grade B of quality of evidence), while ATICE, MSAT, and VICS scales are moderately valid and reliable.

Both SAS and RASS explore the domain of consciousness, typically ranging from alert to comatose, and are graduated according to the response to a stimulus of

**Table 5.1** Ramsay Sedation Scale (RSS)

Score	Definition
1	Anxious and agitated or restless or both
2	Cooperative, oriented, and tranquil
3	Responds to commands only
4	Brisk response to a light glabellar tap or loud auditory stimulus
5	Sluggish response to a light glabellar tap or loud auditory stimulus
6	No response to a light glabellar tap or loud auditory stimulus

Performed using a series of steps: observation of behavior (score 1 or 2), followed (if necessary) by assessment of response to voice (score 3), followed (if necessary) by assessment of response to loud auditory stimulus or light glabellar tap (score 4–6) (Modified from Ramsey et al. [2]), Permission obtained from “Wolters Kluwer Health, Inc.”

increasing intensity, first the verbal and then the physical one. In addition, both scales evaluate the degree of agitation based on the observation of spontaneous patient behavior, graduated from slightly agitated to aggressive and dangerous. The SAS consists of seven levels (see Table 5.2): three levels of agitation (from 7 to 5), a calm and cooperative level (level 4), and three levels of sedation (from 3 to 1). The RASS (see Table 5.3) is a ten-level scale: four levels of agitation (from +1 to +4), a level of calm and alert (level 0), and five levels of sedation (from −1 to −5) defined by response to the stimulus. RASS also includes an assessment of higher and better-defined levels of consciousness such as cognition or sustainability defined by the ability to maintain visual contact with the examiner or lack of visual contact but

**Table 5.2** Sedation-Agitation Scale (SAS)

Score	Term	Description
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bed rail, striking at staff, thrashing side to side
6	Very agitated	Does not calm down, despite frequent verbal reminding of limits; requires physical restraints, biting endotracheal tube
5	Agitated	Anxious or mildly agitated, calms down to verbal instruction
4	Calm and cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Modified from Riker et al. [10], Permission obtained from Wolters Kluwer Health, Inc.

**Table 5.3** Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative or violent, immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or exhibits aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (>10 s) awakening, with eye contact, to voice
−2	Light sedation	Not fully alert, but has sustained (>10 s) awakening, with eye contact, to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Performed using a series of steps: observation of behaviors (score +4 to 0), followed (if necessary) by assessment of response to voice (score −1 to −3), followed (if necessary) by assessment of response to physical stimulation such as shaking the shoulder, and then rubbing the sternum if no response to shaking the shoulder (score −4 to −5) (Modified from Sessler [11], Permission obtained from American Thoracic Society)

**Table 5.4** Sedation/  
Agitation level according to  
RASS or SAS scales

Level of agitation/sedation	RASS	SAS
Agitated	From +1 to +4	From 5 to 7
Awake and calm	0	4
Lightly sedated	From −1 to −2	3
Deeply sedated	From −3 to −5	From 2 to 1

presence of movements to the examiner's voice [12]. In particular, RASS has precise, unambiguous definition for levels of sedation in contrast to SAS or other scales in which each sedation level requires a combination of several responses and/or the selection of one criterion among many others. These features should increase the discriminative power between the different levels and reduce the subjectivity.

Clinical scales should be always administered using a rigorous and logical procedure to evaluate the response to the increasing stimulus. It is the so-called step-wise assessment: first observation of behaviors followed by assessment of response to voice and then to physical stimulation from the lighter stimulus, such as shaking the shoulder, and then to more painful such as rubbing the sternum if no response.

So according to PAD 2013, the level of agitation or sedation is defined as (see Table 5.4): *agitated* for RASS from +1 to +4 or SAS from 5 to 7, *awake* and calm if RASS 0 or SAS 4, *lightly sedated* if RASS from −1 to −2 or SAS = 3, and *deeply sedated* if RASS from −3 to −5 or SAS from 2 to 1.

Sedation scales can be administered to all adult ICU patients, sedated or not, intubated or non-intubated. Special care should be taken when evaluating patients with hearing problems and visual loss for RASS, who do not understand the language, and quadriplegic patients. They cannot be applied in curarized patients.

Subjective monitoring should be a part of routine bedside evaluation by nurses, administered at least every 8 h along the German guidelines (DAS) until  $\geq 4 \times$ /shift as endorsed by PAD 2013 [13]. The ICU staff should regularly redefine sedation goal or end point; the current status should be frequently assessed, reevaluated if necessary, as well as systematically documented (grade 1B).

The proper and regular use of sedation scales allows timely identification and treatment of underlying causes of sudden changes of consciousness and thus is an integral component of most patient-focused management algorithms of analgesia, sedation and delirium, sleep, and anxiety management.

As outlined in DAS guidelines, actual clinical scales do not properly evaluate anxiety, and agitation is not a substitute content since a patient can be calm and cooperative but in anxious state. Short versions of standard psychological instrument (e.g., State-Trait Anxiety Inventory) could be tested in ICU. The creation of a validated anxiety scale is desirable. The latest eCASH strategy suggests that sedation should be minimised, as early as possible, and, through the use of analgesia and human interaction, the patient is kept calm, cooperative, and comfortable. In this condition, the rating of anxiety would be even greater important than now [14].

Over the past 15 years, the routine use of sedation scales has increased along with implementation of sedation guidelines, protocols, and a shift toward analgo-sedation policies. A review of German hospitals showed increases in the use of

sedation scales from 8 to 51% over the period of 2002–2006 [15]. Also, recent surveys in France and Belgium confirm, respectively, a 68% and 86% availability of a sedation scale [16, 17]. While in Europe the RSS is still the most used scale, in English-speaking countries a general shift away from using the RSS is already observed. More recent surveys report that the most common instruments are RASS (38%) and SAS (28%) in Australia and New Zealand [18], while RASS is most used (65%) in the UK [19].

Despite these remarkable changes, surveys conducted in various countries have shown that the depth of sedation frequently goes unmonitored, many patients are not daily evaluated, and sedation protocols are not widely adopted [20].

More efforts need to close the gap between the evidence highlighted in the guidelines and ICU practice.

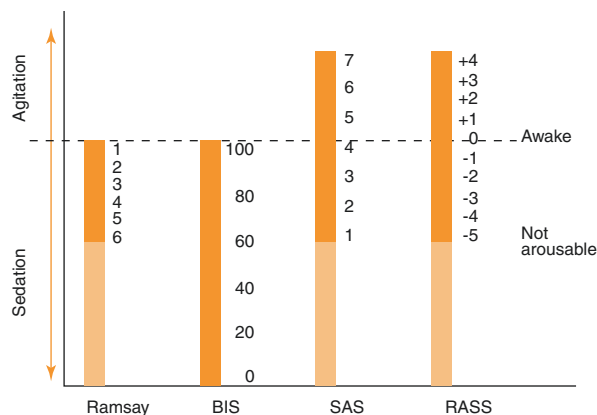
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### 5.3 Objective Monitoring

The target organ of sedatives is the brain, and the electroencephalogram (EEG) changes consistently, predictably, and in a characteristic manner with increasing of sedation. Full EEG analysis is informative but requires expertise, is time-consuming, and is costly. Moreover it cannot deliver real-time informations. Over the last 20 years, various quantitative electroencephalogram (qEEG) monitors have been created such as BIS monitor (Medtronic), E-Entropy monitor (GE Healthcare), Narcotrend-Compact M monitor (MT MonitorTechnik), and recently SedLine monitor (Masimo). They digitally acquire the raw EEG at forehead site and through complex statistical modeling techniques generate a number that is used to indicate the patient's response to anesthetic drugs during surgery. The dimensionless number varies from 0 to 100, where 0 corresponds to a flat EEG, that is, completely suppressed electrical activity, and 100 is the EEG of a fully awake patient. Each monitor indicates numerical ranges that correlate to sedation level. For most devices, the interval 100–80 correlates to fully awake/minimally sedated, 80–60 to light/moderate sedation, 60–40 to loss of consciousness (LOC) (i.e., the general anesthesia ideal plane), and <40 oversedation. For SedLine, 50–25 correlates to LOC plane. The purpose of this chapter is not to describe each monitor in detail and the following considerations can be applied to all qEEGs.

So, the qEEGs provide a simple, objective, and noninvasive way of monitoring the function of the primary target of anesthetic drugs. In 2012 the National Institute for Health and Clinical Excellence (NICE) recommended their use to aid the tailoring of anesthetic dose to the individual patients, to avoid inadequate (awareness) or excessively deep levels of anesthesia (oversedation) in operatory room [21]. The availability of a number, provided automatically, in real time, at bedside makes these monitors particularly attractive in intensive care for objective and continuous monitoring of sedation in ICU [21]. Moreover, the qEEGs cannot be replaced by clinical scales since the latter are not able to measure the degree of suppression of brain activity below the LOC, i.e., RASS <3 or SAS <2, and even more when the patient is paralyzed. The artifacts due to movements in a lightly or moderately

**Fig. 5.1** Clinical sedation scales possess optimal range from agitated to sedated patient. They do not completely cover the BIS range, which allows for discrimination of deeper sedation states (modified from Tonner et al. [22], Permission obtained from Elsevier)



sedated patient can alter the EEG trace, introducing frequencies (i.e., waves) that mimic the awake state and falsely elevate the number. Thus, compared to sedation clinical scales, qEEGs offer a higher degree of reliability with deeper states when artifacts are less likely to occur [22] (Fig. 5.1).

For these reasons, along PAD 2013 guidelines, the main indication for their use is as adjunct to subjective sedation scales in unparalyzed patients (grade 1B) and as the main monitoring in paralyzed patients (grade 2B).

However qEEG number can vary greatly in ICU patients.

Clinical activity, electrical interference from instrumentation such as monitor, electric bed, and warming device, can elevate the qEEG number. The electrode adhesion to the forehead skin can be reduced (sweating, tissue edema, electrode drying) determining impedance alterations and consequent reduction of the quality of raw EEG recorded. Finally, in altered physiological conditions (e.g., hypotension, hypoglycemia, hypothermia) and underlying cerebral pathologies (e.g., dementia, vasculopathy, brain failure, or multi-organ-related encephalopathy), EEG rhythms are similar to that observed during deep sedation, and usually the qEEG number is reduced [23]. Therefore, particularly in ICU, frequent and different conditions could result in a qEEG number indicating an incorrect sedation state.

For these reasons, many clinicians consider this monitoring as “a random number” also discouraged by literature that has so far failed to demonstrate its utility in ICU [24].

However, as Bennet et al. pointed out, “many of the factors that can mislead the qEEG can be readily identified by scrutiny of the raw EEG” [25], and the knowledge of the main brain waves combined with their recognition on the raw EEG trace allows to establish the correspondence between the number qEEG, EEG trace, and the effective grade of EEG cortical suppression correlated to each level of sedation.

In addition, as these monitors have been created and validated only on individuals with healthy brain, we can separate patients to be monitored in two categories according to the initial brain conditions: postoperative patients/early ICU admission and long-staying ICU patients.

### 5.3.1 Postoperative Patients/Early ICU Admission

Once the abnormal physiological conditions (e.g., hypotension) are corrected and if the starting brain conditions are not altered (e.g., head trauma or brain failure), we can reproduce monitoring conditions similar to those of the operating room and get valid indications to titrate sedation. The number automatically provided by the monitoring is sufficiently valid in paralyzed and deeply sedated patients, with minimal or without EMG activity. However external artifacts can occur misleading the number. Firstly, the number should be scrutinized and interpreted and secondly interpreted according to the hypnotic drug used or the combination of hypnotic/analgesic used.

#### 1. How to Correctly Interpret a qEEG Number

EEG waves are mainly described by their frequency (number of waves in the time unit, i.e., 1 s) (see Fig. 5.2).

Observing EEG from awake patient to LOC to oversedation, we can identify wave modifications in frequency and amplitude as occur during sedation and that are typically generated by hypnotics acting on GABA systems (propofol, pentobarbital, anesthetic gas, benzodiazepine) [26] (see Fig. 5.3). In the awake patient, with eyes closed, the rhythm is fast (gamma/beta2 waves), with very low voltage, and the EEG baseline oscillates minimally due to eye movement. Larger baseline deflections appear at the end of the EEG trace due to blinking (see Fig. 5.3a). In minimal sedation rhythms increase voltage but are still at high frequency (beta waves) (see Fig. 5.3b). In moderate sedation and initial transition to the LOC, the waves are slower and larger (theta and delta), fragmented together, and the baseline begins to oscillate more widely (Fig. 5.3c). At LOC typically the delta waves give the appearance of rhythmic, wide, and slow EEG oscillation on which are inserted faster and less amplitude waves (alpha-like/spindle) (see Fig. 5.3d). Along Bennet et al., the presence of alpha-like/spindle waves and background slow waves, with no fast waves, is probably the most important EEG sign of anesthesia plane.

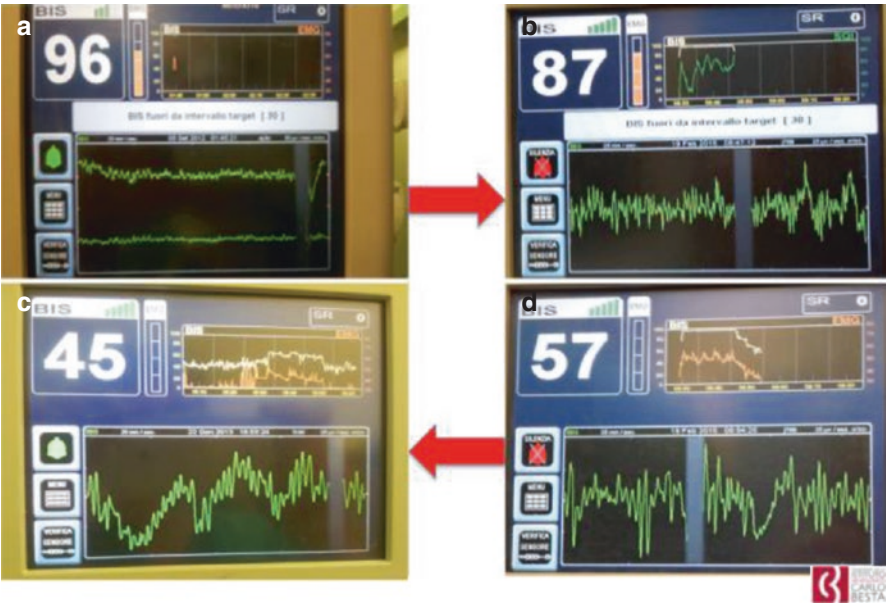
During oversedation the spindle disappear, and the delta waves became wider until to the burst suppression rhythm that is typically flat interrupted by fires of waves (see Fig. 5.4, top left). The further increase in sedation results in cortical suppression with flat EEG (Fig. 5.4 at bottom right).

Table 1. Electroencephalogram wave categorization by frequency

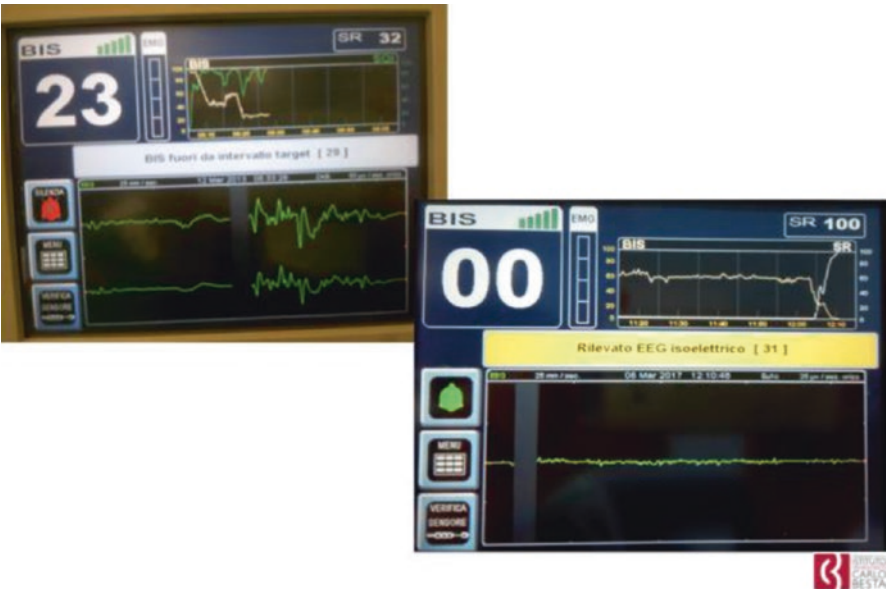
Wave category	Descriptive term	Frequency (Hz)
$\delta$	Slow	0.5-3.5
$\theta$	Slow/medium	3.5-7.0
$\alpha$ /spindles	Medium	7.0-13.0
$\beta$	Fast	13.0-30.0
$\gamma$ / $\beta$ 2	Fast	30.0-80.0

**Fig. 5.2** EEG waves (Reprinted from Bennet et al. [25], Permission obtained from Wolters Kluwer Health, Inc.)





**Fig. 5.3** Typical EEG modifications from awake to LOC with GABA hypnotics. (a) Awake, (b) minimally sedated, (c) deeper sedated with transition to LOC, (d) at LOC

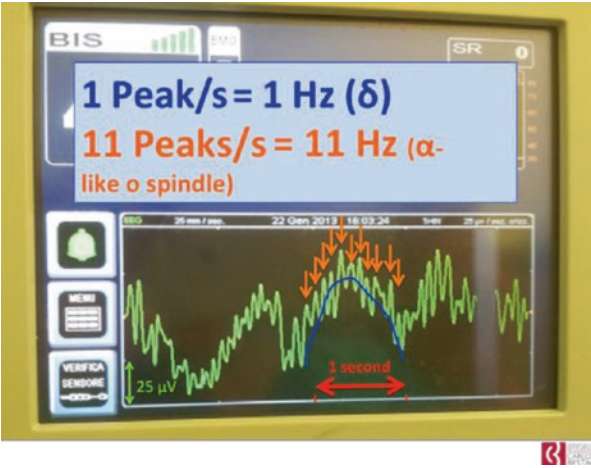


**Fig. 5.4** EEG during oversedation. Burst suppression rhythm (to the top left) and flat EEG (bottom right)



Therefore, the EEG rhythm at LOC is characteristic and unmistakable (delta + alpha-like/spindle) and easily memorable (see Fig. 5.5).

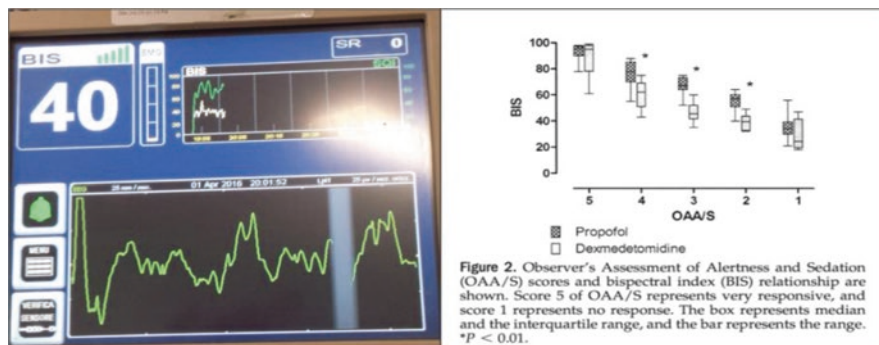
If the LOC rhythm is not easily identifiable (Fig. 5.6), the filter elimination from the trace allows to highlight typical delta waves (see Fig. 5.6). Thus, to ameliorate the wave recognition, it is important to display the EEG trace with higher resolution as possible and without filters [27].



**Fig. 5.5** EEG rhythm at LOC is delta + spindle. The blue line identifies the delta wave (1 peak/s); the orange arrows identify the alpha-like/spindle (11 peaks/s) waves. The delta voltage is much higher than those of alpha-like/spindle



**Fig. 5.6** EEG at LOC with (left) and without (right) filters



**Fig. 5.7** Left: The dexmedetomidine EEG at LOC is constituted of delta waves without alpha-like/spindle. Right: The qEEG values are always lower for the same levels of consciousness in respect to propofol (Reprinted from Kasuya et al. [28], Permission obtained from Wolters Kluwer Health, Inc.)

The EEG and qEEG rhythms at LOC differ when non-GABA drugs are used. As well described by Brown et al. [26], ketamine acts through NMDA circuits leading to aberrant excitatory activity in the cortex and subcortical areas. Rapid waves (beta) appear on EEG at LOC similar to that seen in light sedation (Fig. 5.3b). Alpha2 agonists, such as clonidine and dexmedetomidine, act on subcortical circuits, proximal to locus ceruleus. The EEG resembles that of deep sleep at stage N3, i.e., only delta waves (see Fig. 5.7, left). Therefore with ketamine the qEEG value at LOC is higher than that recommended, and the increase of sedation could lead to oversedation. On the opposite, with dexmedetomidine the qEEG values are lower for the same level of sedation seen in GABAergic hypnotics (Fig. 5.7, right) [28]. Thus, decreasing sedation according to the qEEG number could lead to dangerous undersedation.

As already demonstrated, the recognition of EEG rhythms is simple, learning is fast (15 min of tutorial) and allows to verify the qEEG number [29].

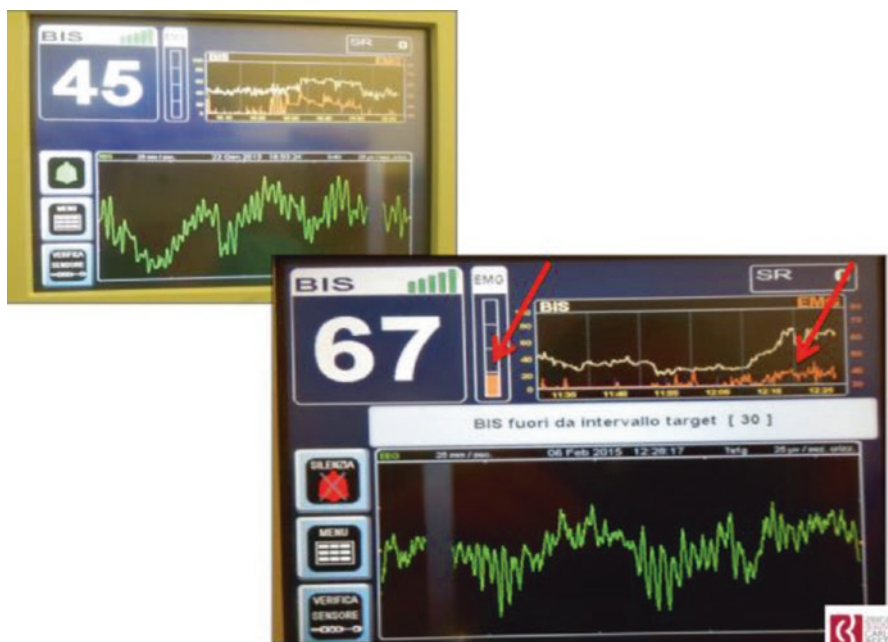
It will not be difficult now to recognize an EEG rhythm even in the presence of artifacts and whether or not the qEEG number is consistent with the appearance of the raw EEG signal.

In the three following cases, the number indicates higher level of sedation than the real one.

First, in Fig. 5.8, the raw EEG is delta + alpha-like/spindle rhythm typical of LOC in both images. However, the qEEG number is incorrectly higher at the bottom because of contamination from EMG (see the EMG bar and red line on trend display). The EMG introduces small-amplitude and high-frequency waves that falsely increase the qEEG number.

Second, in Fig. 5.9, after turning on the fluid heater, wide-voltage, pointed, and atypical waves appear on the LOC EEG rhythm, and the qEEG number increases.

Third, a burst suppression rhythm is present in both photographs of Fig. 5.10. On the left, the rhythm is not contaminated, while on the right the small-amplitude and high-frequency waves are visible on the flat portion of the burst suppression rhythm



**Fig. 5.8** Delta + alpha-like/spindle rhythm at LOC consistent with qEEG number (top) and incoherent with artifacts from EMG (bottom). The red arrows on the EMG display and trend line indicate EMG



**Fig. 5.9** Delta + alpha-like/spindle rhythm of LOC consistent qEEG number (left) and incoherent with artifacts (red arrows) created by turning on a fluid warmer (right)

that increase the qEEG number. Also, the SR (suppression rate), i.e., the percentage of flat EEG in the unit of time (usually 60 s), is falsely low.

Thus the “contaminated” qEEG numbers in Figs. 5.8 and 5.9 would indicate undersedation, while the EEG restores the correct diagnosis of LOC. The increase



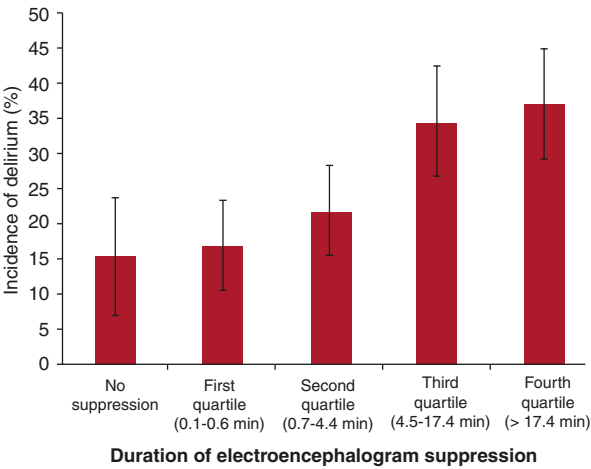
**Fig. 5.10** Burst suppression rhythm without artifacts (left) and with artifacts (right) created by a coagulator. The small and rapid frequency waves on the flat portion of EEG falsely increase the qEEG number. Their presence is signaled by the red signal increasing on the EMG bar and is recognizable on the trend. The red circle highlights the SR

of sedation could lead to oversedation. On the opposite, in Fig. 5.10, the “contaminated” qEEG indicates LOC, while the raw EEG shows oversedation and indicates the necessity to hypnotic decrease. Burst suppression is associated to an increased incidence of delirium and should be carefully avoided. An observational cohort study conducted in 727 adult postoperative patients admitted to ICU shows that increased duration of raw EEG suppression is associated with increased odds of postoperative delirium (odds ratio (OR) for log of minutes of suppression, 1.22; 99% CI, 1.06–1.40;  $P = 0.0002$ ) (see Fig. 5.11) [30]. Another observational study in 124 patients directly admitted to ICU and deeply sedated shows that time in burst suppression, as measured by processed EEG (BIS <40), is an independent predictor of incidence and time to resolution of post-coma/post-deep sedation delirium (Fig. 5.12). The OR for incidence of delirium is 4 after 1 h passed in suppression, and recovery to the preexisting cognitive state is precluded after 400 min of suppression [31].

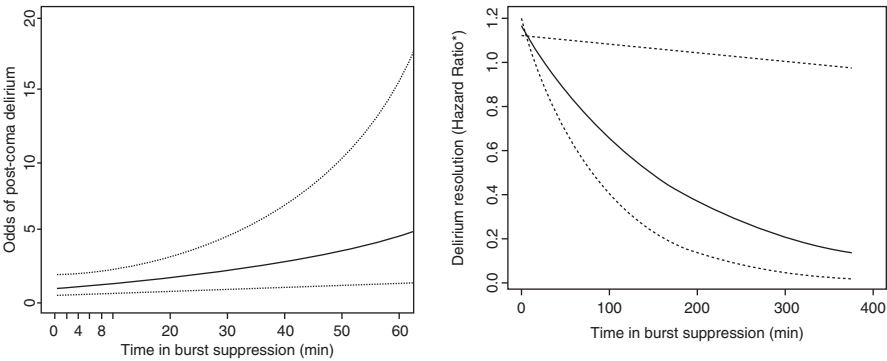
Elderly patients are significantly at risk of delirium. Their anesthetic needs can be up to half those used in younger patients for the same sedation level, and burst suppression rhythm more frequently occurs [32].

Opposite to the three previous conditions, in the three following cases, the qEEG number indicates lower level of sedation than the real one.

First, Schuller et al. administered curare to ten fully awake volunteers and showed that BIS decreases in response to neuromuscular block alone [33].



**Fig. 5.11** Patients who experienced longer suppression were more likely to experience postoperative delirium (Reprinted from Fritz et al. [30], Permission obtained from Wolters Kluwer Health, Inc.)



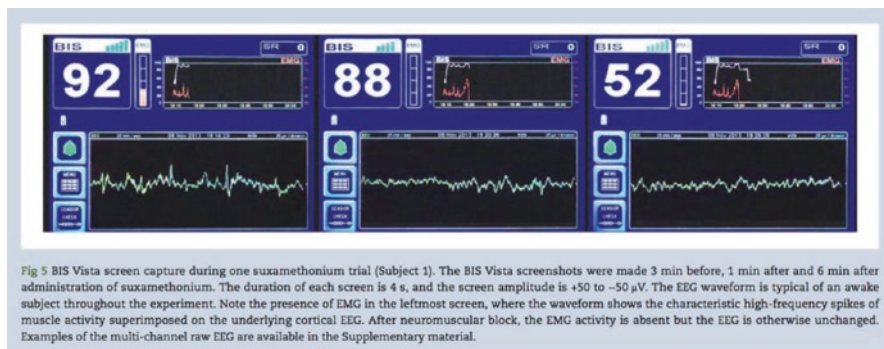
**Fig. 5.12** After 1 h in burst suppression, the OR for incidence of delirium is 4 (left side). After 400 min in burst suppression, the patient remains in delirium (Reprinted from Andersen et al. [31], Permission obtained from Wolters Kluwer Health, Inc.)

However, the raw EEG remained unchanged with gamma/beta2 waves of awake state (see Fig. 5.13). The disappearing of the electromyographic gamma/beta2 components is mistakenly interpreted by the BIS algorithm as initial sedation state (see Fig. 5.3 or 5.4).

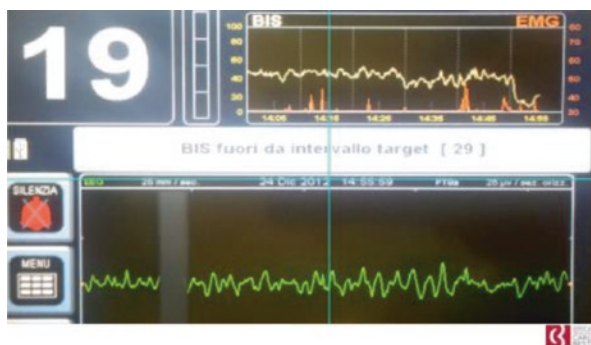
Second, a patient perfectly relaxed, pain-free, with closed eyes, and contactable was successfully extubated at the end of case at BIS of 19 at our institute. The raw EEG shows an alpha rhythm. EMG is absent, and then there are no gamma/beta2 waves typical of the fully awake state. Probably the algorithm failed since it elaborated with the EEGs of fully awake patients (Fig. 5.14).

Third, as Dahaba pointed out, 5–10% of the population has a genetically determined low-amplitude EEG (<20  $\mu$ V) not associated with any brain dysfunction [23].





**Fig. 5.13** Awake EEG (with gamma/beta2 waves) inconsistent with qEEG during neuromuscular blockade (Reprinted from Schuller et al. [33], Permission obtained from Oxford University Press)

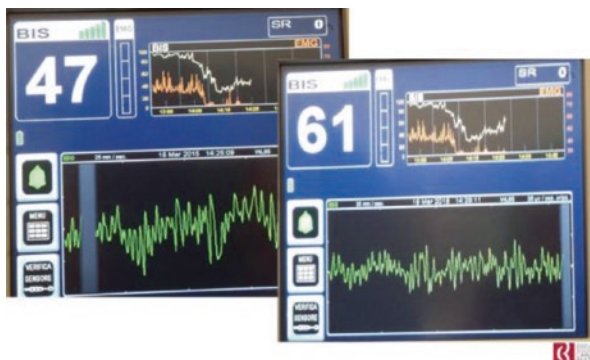


**Fig. 5.14** Raw EEG with alpha waves of a relaxed patient, with eyes closed and able to follow commands, inconsistent with qEEG number

The qEEG can interpret the EEG as suppressed resulting in low qEEG with a fully awake patient.

### 5.3.2 qEEG Number and Interaction with Opioids

The acceptable qEEG value for a given sedation level may vary if an analgesic is added. In ICU usually opioids are administered in adjunct to hypnotics. Opioids predominantly affect noncortical structures and produce minimal or no EEG alterations. Their addition enhances the hypnotic effect allowing to achieve a level of sedation at higher qEEG values with a lower dosage of hypnotic. Because the qEEG is relatively insensitive to opioids, the target value for general anesthesia increases as the opioid component of the anesthetic increases. So it has been suggested that a higher qEEG (e.g., BIS value of >60 at LOC) may be acceptable when a high-dose opioid and low-dose hypnotic combination is used [34].



**Fig. 5.15** qEEG increases after a painful stimulation from 47 to 61. The raw EEG path is modified by delta + alpha-like/spindle to EEG without delta waves with faster ( $>12$  Hz) waves similar to those of lighter sedation. The painful stimulus activated the cerebral cortex



**Fig. 5.16** Trend BIS (i.e., the numerical sequence in the time of qEEG values) remains stable (red arrows) after painful stimulation (intubation and vascular accesses)

As noted in the review of Coleman et al. [35], studies in the ICU demonstrate an increase in the BIS value during routine nociceptive procedures, such as endotracheal suctioning and mobilization (see Fig. 5.15). Some studies, as reported in Coleman et al. review, also show that an analgesic treatment counteracts this increase in the BIS (see Fig. 5.16).

Although promising, scientific evidence is not yet sufficient to conclude on BIS validity in assessing pain, and further studies are needed.

As NICE 2012 stated, after proper training and robust daily experience in the various clinical conditions, the monitoring can be used with greater validity, reliability, and feasibility specially to avoid overdoses of hypnotics. According to the experience of American nurses in pediatric intensive care, qEEG monitoring is a useful tool

as an adjunct to sedation scale assessment, increasing safety and facilitating communication not only between caregivers but also with family members [36].

## 5.4 Long-Stay ICU Patients

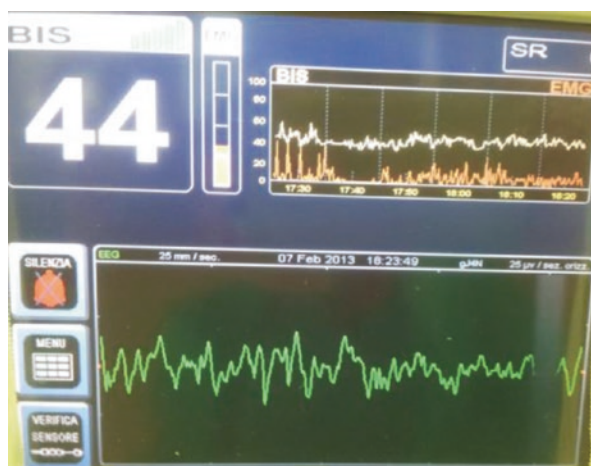
Prolonged deep sedation as well as systemic pathologies can cause brain dysfunction through various mechanisms such as the direct alteration of cell brain function and of the blood–brain barrier and the reduction of blood flow to the brain. The results are synaptic, neurochemical disturbances and neuronal apoptosis [37, 38].

Thus, in these patients the objective sedation monitoring is strongly affected by pathological conditions that alter brain structure and function. Further studies are needed to establish significance and usefulness of EEG monitoring.

The brain rhythms are completely subverted with prevalence (up to 80% of cases) of delta and theta slow waves and alpha reduction, whether the patient is in coma or in a state of delirium or delirium-free [39–41]. The slow rhythms return a qEEG value similar to that of deep sedation of LOC (see Fig. 5.17).

In septic patients there are both slow waves and EEG abnormalities sometimes nonclinically or clinically evident, such as periodic discharge (PD), nonconvulsive seizures (NCS) (see Fig. 5.18) [42]. If the abnormalities occur suddenly, are widespread, and present in the frontal area, slow waves will appear on EEG, while the qEEG number changes in a variable manner depending on the frequency of the starting rhythm and spikes.

PAD 2013 recommend to use EEG monitoring to monitor nonconvulsive seizure activity in ICU patient at risk for seizures (grade 1A). Seizure in paralyzed or

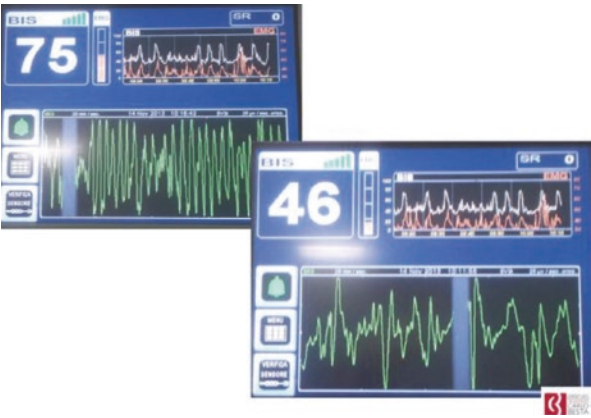


**Fig. 5.17** Ritmo theta/delta in brain failure. See differences with delta + alpha-like/spindle EEG of LOC as in the normal brain at the same qEEG number. The patient may be comatose, delirious, or delirium-free



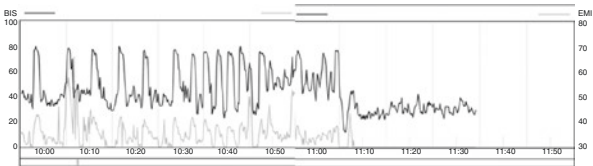


**Fig. 5.18** Periodic discharge (PD) in septic patient (Reprinted from Azabou et al. [41])



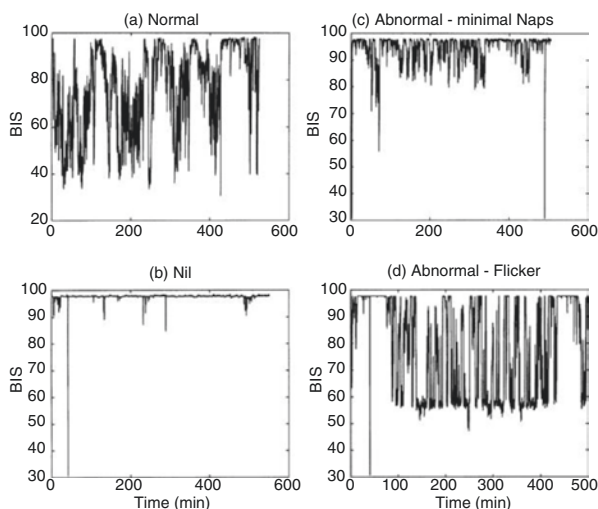
**Fig. 5.19** A case of seizure and postictal state: Fast, sharp, and frequent waves during epileptic seizures (top left). Slow delta and theta waves in postictal (bottom right). In the postictal state, the patient was contactable and executed simple orders

**Fig. 5.20** The trend has a typical “comb teeth” aspect that stabilizes with the resolution of status epilepticus



unparalyzed patients can be easily detected: the qEEG number changes suddenly, and the EEG shows a rapid change of rhythm (see Figs. 5.19 and 5.20).

Critically ill patients have severe sleep disruption and atypical PSG findings [43]. Since preliminary studies in healthy subjects had shown BIS ability to describe natural sleep and good correlation with sleep stages, Nicholson et al. used BIS to study sleep in ICU patients. He found that BIS can roughly describe patterns similar to natural sleep and that a BIS <60 is useful in identifying deep sleep stage (i.e.,



**Fig. 5.21** Examples of four typical sleep patterns of BIS found in ICU. (a) normal, (b) no sleep, (c) minimal naps, (d) abnormal “flickering” (Reprinted from Nicholson et al. [44], Permission obtained from Critical Care Resuscitation)

N3). However, in most patients the sleep patterns are abnormal (see Fig. 5.21) [44]. A subsequent study confirmed that a BIS cutoff  $<55$  identifies the N3 phase of deep sleep with good accuracy [45]. Further studies are needed to determine whether the BIS is useful for describing normal sleep in ICU, quantifying the restorative N3 deep sleep, and checking when alterations occur.

Finally, along PAD 2013 BIS is indicated to titrate burst suppression therapy in ICU patients with elevated intracranial pressure (grade 1A), for example, to a BIS  $<15$ , although not with a 100% accuracy [46]. The patterns should periodically be checked using a complete EEG [46, 47].

Therefore, in this population of patients, objective monitoring is more likely to monitor brain failure than sedation. But we are only at the dawn of an age that needs to be discovered.

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## 6.1 Introduction

Critically ill patients require sedation to optimize patient comfort, facilitate patient-ventilator synchrony, and allow tolerance to procedures. The level of sedation required may change during a patient's stay, depending on the intensity of care, organ support, the course of their disease or healing, and also on the external environment and the time of the day [1]. An optimal degree of sedation is important to avoid oversedation and to reduce the incidence of delirium, length of mechanical ventilation, and length of stay in the ICU [2, 3].

Before the 1980s, the sedation practice and drug selection for adult ICU patients were represented by an extension of general anesthesia [4]. Usually the goal was to achieve a deep sedation, while neuromuscular blocker use was not uncommon [5]. Before the entry of propofol and benzodiazepines into clinical practice, the drugs available for sedation were hypnotics and neuroleptics and—especially in combination—analgesics. The lack of short-acting drugs and the frequent incidence of side effects often led to an administration of a cocktail of drugs, the so-called “lytic solution” or “lytic cocktail,” with the aim of reducing side effects. The lytic cocktail was composed of a mixture of 100 mg meperidine, 50 mg promethazine, and 0.6 mg dihydroergotamine or 50 mg chlorpromazine. This cocktail had been used for more than 20 years for sedation of adult and pediatric patients before general anesthesia or in a non-operating room setting [6]. The lytic cocktail is also known as an “ataractic mixture,” which is defined as a combination of drugs that creates a feeling of “serenity” when administered to patients. The phenothiazines were believed to be useful as anesthetic premedications because of their sedative and vasodilator effects [7]. The

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combination of a narcotic with a phenothiazine provides an analgesic base, lowers blood pressure, and blunts the pressor responses to pain, while inducing deep sedation. Antihistaminic agents were demonstrated to potentiate the sedative and hypnotic effects of the barbiturates [8, 9] and the analgesic effects of opioids [10–12], so that opioids could be used in the short term in dosages that were not associated with respiratory depression. Toxicity associated with this combination manifested as a profound lethargy that persisted long after the clearance of meperidine, accompanied by a decrease in respiratory rate, a decrease in systolic blood pressure, and severe mental debilitation. Even in the work of Laborit and Huguenard [13], who first described the lytic cocktail, this induced state of “artificial hibernation” was associated with considerable cardiovascular instability and prolonged depression of consciousness.

The ideal sedative or analgesic should be characterized by a short onset time of action, should be easy to administer and to titrate in order to produce effective sedation, reproducible in dosage to obtain a similar clinical goal in a large and varied population, predictable in clinical and side effects, and free from severe adverse effects on hemodynamic conditions or respiratory function. Furthermore, its metabolism should not be affected by impaired liver or renal function, any drug interactions or augmented volume of distribution (often seen in critically ill patients), and it should not be protein bound; finally, its offset time should be short enough to rapidly reverse sedation in case of need without any context-sensitive half-life or long-term adverse effects. In the last decade, several new drugs have been developed, some of which perform very close to these ideal features but none of the available medications meets all of them in a single agent, so far. For these reasons critically ill patients are usually given analgesia and sedation that consists of some combination of two or more drugs, a sedative/hypnotic and an analgesic [14–17].

In terms of pharmacokinetics (PK), critically ill patients are quite different from the young, healthy subjects in whom drugs are studied and developed: volume of distribution is generally augmented; liver and/or renal function can be impaired to some extent and so drug metabolism can be affected as a result; plasma protein concentrations can be lowered and the drug-free fraction can increase. These alterations from normal physiology vary throughout the ICU stay and the course of the illness, and ICU physicians have to know and possibly predict alterations in the patients in their charge.

The aim of this chapter is to review the pharmacology, in terms of PK, pharmacodynamic (PD), and pharmacogenetic factors, of the most commonly used sedatives (propofol, benzodiazepines,  $\alpha_2$ -agonists) and opioid analgesics; in particular we focus on factors to be considered by clinicians in order to get the optimal amount of analgo-sedation to improve patient outcome and safety.

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## 6.2 Pharmacologic Principles

In order to prescribe a good analgesic and sedative regimen for a critically ill patient it is important to be aware of several important pharmacologic principles. Briefly, PK describes what the body does to a drug (absorption, distribution, metabolism,



excretion); at the opposite side, PD tells what a drug does to the patient, in term of mechanism of action.

PK is the relationship between the drug dose administered and the concentration at plasma or effector site, after absorption and distribution are completed; this ratio is termed “volume of distribution” ( $V_d$ ) and, together with drug clearance, it is the PK parameter that most affects drug response and safety. The distribution of a drug throughout plasma and tissues can be viewed as a process of dilution from the highly concentrated solution in the syringe to the dilute concentration in plasma. This dilution follows the mixing of drug into blood and transfer into tissues: the distribution will be the result of different rates of solubility between compartments and tissue binding, different capacities for the drug to cross barriers, regional blood flow, and plasma protein binding. Agents that are lipophilic easily cross barriers and cellular membranes and so have a very high  $V_d$  because of sequestration into fat tissue; conversely, hydrophilic opioids like morphine do not penetrate fat tissue and remain within plasma, with a relative low  $V_d$  [18, 19]. Clearance describes the body’s capacity to remove drug, regardless of whether there is any drug in the body. Systemic clearance permanently removes drug from the body, either by eliminating the parent molecule or by transforming it into metabolites: these processes can occur in several different organs, mainly the liver but also the kidneys, lungs, and unspecific tissues. Intercompartmental clearance moves drug between plasma and peripheral tissues. Each agent is eliminated, unchanged or not, by a specific metabolic pathway. Clearance is defined in units of flow, that is, the volume completely cleared of drug per unit of time. Most anesthetic drugs are cleared by hepatic biotransformation; the liver metabolizes drugs through oxidation, reduction, hydrolysis, or conjugation. Oxidation and reduction occur in the cytochrome P450 system as an activating phase, prior to a second-phase reaction. These enzymes can be induced by exposure to certain drugs and increase the liver’s intrinsic metabolic capacity. On the other hand, drugs or hepatic disease can inhibit these enzymes. Conjugation and hydrolysis occur as a second-phase metabolism: conjugation to glucuronic acid is to transform hydrophobic molecules into water-soluble molecules through the addition of polar groups and thus render the metabolites easier to excrete via the kidneys. These compounds are mostly inactive except for the metabolites of morphine, morphine 1-glucuronide and morphine 6-glucuronide, which are as potent as the parent drug. The kidneys clear drug from plasma by filtration at the glomerulus and direct transport into the tubules: they can filter the active and unbound drug or an inactivated metabolite: renal blood flow and creatinine clearance (intended as a glomerular filtration rate index) are correlated with age, gender, and sex as predicted by the Cockcroft and Gault equation [20]. Other tissues, such as plasma, muscle, or lungs, are responsible for drug clearance: for example, the short-acting opioid remifentanyl is metabolized by nonspecific esterases in several tissues; succinylcholine’s molecules are broken down by pseudocholinesterase; spontaneous degradation from the Hofmann reaction occurs in plasma for *cis*-atracurium and atracurium. Finally, distribution clearance is the transfer of drug between plasma and peripheral tissues, and it depends on cardiac function and regional blood flow, administration route, drug tissue solubility, and plasma protein binding. Unlike



metabolic clearance, distribution clearance does not permanently remove drug from the body and it is clinically relevant mostly after a single bolus infusion.

Organ and tissue clearance can be flow limited, capacity limited, or both; plasma clearance can only be capacity limited. Hepatic dysfunction is present in a substantial portion of critically ill patients so that drug clearance can be affected because of reduced liver blood flow (flow-limited metabolism), decreased hepatocellular enzyme activity (capacity-limited metabolism), and decreased bile flow [21, 22]. A combination of the three mechanisms can act simultaneously. During shock, liver is affected by a threefold decrease on blood perfusion: flow-limited metabolism will be reduced to the same extent as for morphine; at the same time, liver hypoperfusion will reduce intracellular oxygen tension and cofactor availability for enzymatic reaction, and capacity-limited clearance will conversely fall [22]. A similar speculation can be made for renal function, which is altered in a large portion of critically ill patients: kidneys excrete non-metabolized agents, active or inactive metabolites, and in case of reduced glomerular filtration rate the clearance will fall and the agent will presumably accumulate.

PK data for sedatives and opioids are, in many cases, derived from studies on single-bolus administrations in healthy adults [22, 23]. It is easy to expect that long-term infusions, instead of a single bolus, will result in different compartment distribution, plasma concentrations, clearance, and half-life. Moreover, results from studies conducted on healthy adults cannot be extended to critically ill patients because of PK parameter alterations, mainly on volume status, third space extension, plasma protein concentration and ligation, and end-organ function impairment; all these deviations from normal physiology will unpredictably affect drug availability, Vd, clearance, and, finally, clinical effect and safety.

PD describes the relationship between plasma and/or site of action of drug concentration and observed clinical response, the latter being determined by drug-receptor binding. In fact, this interaction determines three fundamental PD aspects: the quantitative relationship between a given dose of a drug and the resulting effect (dose-response relationship); the selectivity of a given drug's activity and effect; and the pharmacologic activity of the receptor in terms of agonists, antagonists, and inverse agonists. Receptors therefore serve as a membrane tool that initiates a complex biochemical cascade that determines the agent's pharmacological activity.

Describing the typical dose-response graphic is challenging in critically ill patients because of their previously mentioned PK differences compared with healthy volunteers. The large variability in Vd and impaired drug clearance make particularly unpredictable the concentration at the site of action and, in the addition, the clinical effect of sedatives and opioids can be enhanced by an underlying neurological disease for which the patients is being treated; moreover, objective assessment scales for pain and/or sedation are lacking [18].

Genetics play a substantial role in the pharmacology of sedatives. Several polymorphisms have been described for genes encoding for proteins involved in drug metabolism, transport, intracellular transduction, and PD action. These variabilities account for the large variability in clinical effect for several opioids and sedatives commonly used in critically ill patients [24–27].

### 6.3 Opioid Analgesics

Opioid analgesic medications remain the mainstay of therapy for alleviating pain in the ICU patient [1]. At the same time, opioids also have a role in management of sedation and anxiety, and in facilitating mechanical ventilation. Unrecognized or inadequately treated pain from pathology or ICU procedures creates anxiety in 20–60% of patients [28–30]. Patients mechanically ventilated may be unable to communicate the source of their discomfort and suffer from uncontrolled pain; early assessment for pain is crucial to effectively treat pain-related anxiety in the ICU patient.

Opioids can be classified as naturally occurring, semisynthetic (morphine derivatives in which one of several changes have been made), and synthetic [31] (Table 6.1).

As stated above, most of the available PK information come from data on healthy volunteers after single-dose administration, whereas knowledge on continuous infusion in critically ill patients is lacking.

The intravenous route is preferred in patients whom are unstable; the intramuscular, subcutaneous, or oral routes are, in patient in low perfusion states, subject to unpredictable systemic absorption. In an unstable patient the intravenous route best allows for titration of the drug dose and effect, given the faster onset time and better bioavailability [3].

All opioids are weak bases; this means that when in solution, they dissociate into a free base and a positive-charged proportions, depending on the solution's pH and agent's pKa, with the free-base proportion being more lipid soluble. The speed of onset of opioid effect is affected by both lipid solubility and protein binding, because only the unionized and unbound proportion of the agent constitutes the molecules that are free to diffuse across cellular membranes and compartments to the sites of action. Therefore, low plasma protein concentrations (albumin and  $\alpha$ 1-acid glycoprotein) favor a faster onset time and greater response because of a larger number of unbound molecules.

After intravenous injection, arterial plasma concentrations of opioids rise to a peak within one circulation time. Thereafter, they exhibit a rapid redistribution phase toward peripheral tissues and compartments, followed by an elimination phase; this means that, as described by the compartment model, after a single administration into a central compartment, opioids are either eliminated from the central compartment (by excretion or biotransformation) or are distributed to peripheral compartments. In general, opioids are cleared from plasma by biotransformation in the liver, but extrahepatic metabolism is the sole clearance mechanism for opioids such as remifentanyl.

**Table 6.1** Opioids

Naturally occurring	Semisynthetic	Synthetic
Morphine Codeine	Dihydromorphone/morphinone	Methadone Meperidine Fentanyl Sufentanil Alfentanil Remifentanyl

Opioids are mostly highly lipid soluble, so they are widely and rapidly distributed in body tissues and show, at steady state, a high  $V_d$ ; moreover, after a single bolus administration, their concentration rapidly falls due to redistribution. Opioid uptake by the lungs has implications in opioid PK, so that the time of peak concentration is influenced by the degree of pulmonary uptake. Moreover, pulmonary uptake of opioids can affect the PK of other drugs. It has been shown in cats that pulmonary uptake of propofol is reduced by the administration of fentanyl 30 s before.

Opioids act as agonists binding at specific opioid receptors, widely distributed in the central and peripheral nervous system and in several organ tissues. Opioid receptors are presynaptic or postsynaptic and are found in various regions of the brain and the spinal cord: periaqueductal gray area of the brainstem, amygdala, corpus striatum, thalamus, the medullar substantia gelatinosa (dorsal/posterior horn) in the spinal cord. Receptors have also been described in peripheral tissues in afferent neurons, in the gastrointestinal tract (in the muscle cells within the ileum and colon). Agonists bound to the receptor are able to induce, via a G-protein mechanism and transduction, a hyperpolarization of the cell and decrease in neurotransmission of peripheral nerves and spinal cord; at the same time the brain's perception of pain is diminished. Membrane hyperpolarization leads to a reduction of release of neurotransmitters such as acetylcholine, norepinephrine, dopamine, serotonin, glutamate, and substance P; this mechanism could be synergistically linked to areduction of release of neurotransmitters from presynaptic vesicles [32].

Several types of opioid receptors have been described; the best known and majorly involved in clinical practice are the subtypes  $\mu$ ,  $\delta$ , and  $\kappa$ . Their distribution and clinical effect are briefly described in Table 6.2.

If opioids are used on critically ill patients mainly for pain control, sedation, and tolerance of mechanical ventilation, it should be kept in mind that they have several side effects, including serious adverse reactions (Table 6.3).

A predictable relationship between opioid blood concentration and analgesic and respiratory depressant effects has not been established yet and mechanisms such as tolerance and/or genetic polymorphisms could explain such a wide span of dose regimens needed to reach clinical goals. Given this lack of PK/PD data, ICU clinicians should titrate in a single patient the doses of opioid therapy based on periodic pain assessment or side-effect occurrence, keeping in mind that the maximum amount of opioid administration should be limited only by the presence of adverse events [3, 33].

**Table 6.2** Opioid receptors

Traditional notation		Endogenous ligand	Analgesia	Effects
$\mu$	$\mu_1$	Endorphins	Supraspinal and peripheral	Sedation, euphoria, urinary retention, miosis
	$\mu_2$	Endorphins	Spinal	Depression, bradycardia, physical dependence, gastrointestinal effects, pruritus
$\delta$		Enkephalins	Supraspinal and spinal	Antitussive effect, inhibition of dopamine release
$\kappa_{1,2,3}$		Dynorphins	Supraspinal and spinal	Antitussive effect, dysphoria, miosis, diuresis

**Table 6.3** Clinical side effects of opioids

Neurologic system
<ul style="list-style-type: none"> <li>• Analgesia</li> <li>• Euphoria</li> <li>• Sedation</li> <li>• Psychotomimesis (common in elderly patients)</li> <li>• Seizures</li> </ul>
Cardiovascular system
<ul style="list-style-type: none"> <li>• Hypotension (vasomotor centers and histamine)</li> <li>• Bradycardia</li> <li>• Dysrhythmias (overdose)</li> </ul>
Pulmonary system
<ul style="list-style-type: none"> <li>• Respiratory depression and respiratory acidosis</li> <li>• Antitussive effect</li> <li>• Bronchospasm</li> </ul>
Gastrointestinal system
<ul style="list-style-type: none"> <li>• Nausea and vomiting (5-HT<sub>2</sub> mediated, act on chemoreceptor trigger zone)</li> <li>• Delayed gastric emptying</li> <li>• Constipation</li> <li>• Increased smooth muscle tone (biliary tract, intestinal, pylorus, anal sphincter)</li> </ul>
Dermatologic system
<ul style="list-style-type: none"> <li>• Urticaria</li> <li>• Pruritus (centrally mediated)</li> </ul>
Endocrinologic system
<ul style="list-style-type: none"> <li>• Reduced release of antidiuretic hormone</li> <li>• Reduced release of gonadotropin</li> </ul>
Genitourinary system
<ul style="list-style-type: none"> <li>• Urinary retention</li> <li>• Ureteral spasm</li> <li>• Antidiuresis</li> <li>• Priapism</li> </ul>
Immunologic system
<ul style="list-style-type: none"> <li>• Mast cell degranulation/histamine release</li> <li>• Cytokine stimulation (IL-1)</li> <li>• Rare true allergic reaction</li> </ul>
Musculoskeletal system
Truncal/chest wall rigidity and myoclonus
Maternal/fetal system
<ul style="list-style-type: none"> <li>• Placental transmission</li> <li>• Neonatal blood-brain barrier immature</li> <li>• Neonatal respiratory depression and opioid dependence</li> <li>• Neonatal withdrawal (seizures)</li> </ul>
Ophthalmic system
Miosis

Analgesia from opioids results from modulation of pain perception both at the level of the central nervous system and peripherally; in fact, pain control needs to be considered with the brain circuits modulating analgesia in mind, where a high concentration of opioid receptors is found [34]. At the cortical level, there is a decreased reception of painful sensory inputs and enhanced inhibitory outflow from the brain to the sensory nuclei of the spinal cord, where peripheral afferents entry the spinal cord. This entry is also decreased itself by the neurotransmission from peripheral afferent pain neurons to the spinal cord and from the spinothalamic tract to the brain. On the

**Table 6.4** Physicochemical characteristics, pharmacokinetics, and therapeutic range of opioids in adults

Drug	Morphine	Fentanyl	Sufentanil	Alfentanil	Remifentanyl
Receptor	$\mu, \kappa$	$\mu$	$\mu$	$\mu, \delta, \kappa$	M
pKa (pH 7.4)	7.9	8.4	8.0	6.5	7.26
Protein binding (%)	35	84	93	92	60–90
Elimination half-life (h)	1.5–3	3–7	2–5	1.5	0.15–0.33
Clearance (ml/kg/min)	23	10–20	10–15	3.8	40–60
Metabolism	Phase II conjugation	P450	P450	P450	Blood and tissue esterases
CSHT <sup>a</sup>	Morphine-6-glucuronide, active metabolite	Increasing proportionally to infusion duration (max after 240 min of infusion)	30 min (increasing after 1 h infusion)	60 min	3–4 min
Approximately equianalgesic dose (mg)	10	0.1	0.01	0.75	0.1
MEAC <sup>b</sup> (ng/ml)	10–15	0.6	0.03	15	0.75
Concentration (ng/ml) for spontaneous ventilation	<25	1–3	<0.4	<200	0.3–0.6

<sup>a</sup>Context-sensitive half -life<sup>b</sup>Minimum analgesic concentration (MEAC) ng/ml

one hand opioids act to directly inhibit ascending transmission of nociceptive information from the spinal cord dorsal horn and on the other hand they activate pain control circuits that descend from the midbrain, via the rostral ventromedial medulla (RVM), to the spinal cord dorsal horn. The net effect is decreased perception of nociceptive information at the cortical level [35]. Types of opioid receptors involved at single levels of pain perception are briefly described in Table 6.4.

All opioid agents produce depression of ventilation in a dose-dependent mechanism, which is most deleterious for those patients who are not tracheal intubated and ventilated; moreover, when administered at equianalgesic doses, all opioid agonists lead to a similar degree of respiratory depression [36, 37]. Among the opioid receptors described, the  $\mu_2$  receptors are possibly involved in the development of this side effect; in fact, the stimulation of this subtype  $\mu$  receptor results in a lowered hypercarbic sensitivity and compensatory respiratory drive [38]; at the same time, the hypoxemic response is also depressed. All these pathways lead to progressive bradypnea, hypopnea, or maybe apnea. Opioid susceptibility, in terms of ventilator depression, vary widely among patients; the elderly, COPD patients, and comatose patients are more sensitive to opioid actions [35]. Painful stimuli can revert respiratory depression so that clinicians should be aware of the possibility of depression occurring when procedural pain is over (e.g., drain positioning, surgical stimuli,

fracture, or articular reductions). Moreover, the respiratory side effects of opioids can involve bronchial constriction via histamine release, mostly in atopic patients.

Opioids can cause hypotension; this is the result of peripheral arterial and venous dilation mediated by an increased vagal nerve tonicity, with relative reduction of sympathetic outflow and histamine release [39]. The hypotensive effect is more relevant in patients in whom intravascular volume is reduced, while histamine release is independent of the immune system, not involving the IgE pathway [40]. However, histamine release is not the same for all opioid agents, meperidine or morphine being more affected than sufentanil or fentanyl [41], and the severity of histamine-related hypotension can be reduced by slowing the rate of infusion and optimizing the intravascular volume, especially in those patients considered to be fluid responsive.

Hypotension could come also from bradycardia, most often secondary to increased vagal nerve activity and decreased excitatory stimulation from pain control.

Intravenous (IV) administration of opioids has been associated with motor abnormalities, mainly increased tone of the chest wall and other truncal muscles. This complication is seen when large doses of highly lipophilic opioids (e.g., fentanyl and derivate) are administered rapidly, and it can compromise either spontaneous or bag-valve-mask ventilation. Whereas it was previously thought that opioid actions at the level of the spinal cord were responsible for this effect, it now appears that a central dopaminergic effect may be contributory. Both naloxone and neuromuscular blockade can overcome rigidity. Vocal cord spasm, although rare, can cause closure of the vocal cords, leading to difficult bag-valve-mask ventilation [35].

Tolerance, the mechanism through which the agent's effect decreases despite plasma concentration remaining unchanged, is shared by all opioid agents, and occurs most when they are administered continuously [42, 43]. Tolerance is hard to diagnose; if a patient needs more opioids during an ICU stay it could be because of tolerance or because of an emerging painful stimulus. The mechanism through which tolerance develops over time can involve a genetic pathway and an adaptive increased receptor transcription [42]. Due to their greater receptor affinity, synthetic opioids may result in a greater tolerance development than morphine usually does [43].

Sudden discontinuation of a short half-life opioid, when tolerance has occurred, may result in a withdrawal syndrome, which includes agitation, hypertension, tachypnea, sweating, and even pain that, in a critically ill patient, could be diagnosed as delirium. In fact, opioids may cause hallucinations, agitation, euphoria, and sleep disturbances, and have been associated with the development of delirium [44]. After a long period of continuous opioid infusion a slow decrease in the rate of infusion or the administration of an NMDA (N-methyl-D-aspartate) receptor antagonist such as methadone may help to decrease the chance of onset of a withdrawal syndrome [3, 45, 46].

Specific agents are described in the next sections and briefly outlined in the Table 6.4.

### 6.3.1 Morphine

Morphine PK is largely different from that of synthetic opioids, like fentanyl and similar agents, due to morphine's comparatively low lipid solubility. Low lipid

solubility accounts for the relatively small first-pass uptake of morphine by the lung. Having a  $pK_a$  of 8.0, which is greater than physiologic pH, after intravenous injection only a small fraction (10–20%) of morphine is un-ionized; this means that penetration of morphine across the blood-brain barrier is presumably slower than that of other opioids. Plasma protein binding, mostly albumin, is 20–40%. In the liver, morphine is metabolized mostly by conjugation; morphine 3-glucuronide (M3G) is the major metabolite of the parent agent and it has very little analgesic effect because it does not bind to any opioid receptor. At the other hand, M6G is formed from morphine metabolism in a proportion of 10% and it too has an opioid action; it is a more potent agonist on  $\mu$  receptor than morphine and it plays a substantial role in morphine's analgesic effect, with a similar offset time. M3G and M6G are excreted by the kidneys, and in patients with renal impairment M6G may be responsible for the adverse effects of opioids [47]. Hepatic extraction for morphine is very high: orally administered morphine shows very low bioavailability, 20–30% of that seen after intravenous, subcutaneous, or intramuscular injection. At the same time, it means that in patients with decreased hepatic blood flow (hypoperfusion states) morphine clearance may be reduced [48].

Mainly binding to the  $\mu$  receptor sub type results in typical side effects, some of which, i.e., sedation and respiratory depression, make morphine a good agent for analgo-sedation in the ICU and for increasing mechanical ventilation tolerance, but, at the same time, decreased GI motility, nausea and vomiting, histamine release, and miosis are also seen. Despite its efficacy, morphine has relatively poor penetration into the CNS, largely because of its low lipid solubility.

### 6.3.2 Fentanyl

Fentanyl and similar agents show very high lipid solubility with a consequent very rapid distribution to compartments; typically, a three-compartment model is used to describe fentanyl PK. Shortly after a single bolus injection, plasma concentration rapidly increases; an initial breakdown is seen as a result of compartment distribution, and slower breakdown results from clearance through organ metabolism and body excretion. A single IV injected dose of fentanyl is about 75% taken up in lungs; in the blood compartment, 80% of fentanyl is protein bound, whereas 40% is internalized in red blood cells. The long duration of action of fentanyl is due to peripheral distribution and accumulation; in the liver, it is inactivated by dealkylation and hydroxylation; its metabolite, norfentanyl, is excreted by the kidneys and detected in urine for up to 48 h after injection. Fentanyl extraction by the liver is very high and in patients with decreased hepatic blood flow (hypoperfusion states) fentanyl clearance may be reduced [48].

Fentanyl has a very rapid onset time and short duration of action, especially after a single bolus injection; fentanyl's clinical peak effect occurs 5–7 min after IV administration and this makes fentanyl a good choice for analgesia and sedation with short invasive procedures. After prolonged and continuous infusion, it accumulates in peripheral tissues like lipids, skeletal muscles, and lungs, resulting in a prolonged duration of effect after discontinuation of the infusion. It is to be noted

that fentanyl is affected to a lesser extent from histamine release than morphine, with fewer cardiovascular effects [49]. Muscle rigidity, particularly of the chest wall, may hamper spontaneous or assisted ventilation. This effect may be reversed with naloxone, but this will compromise analgesia efficacy.

### 6.3.3 Alfentanil

Although alfentanil is 90% bound to plasma proteins, its  $pK_a$  of 6.5, which is lower than the plasma pH, allows that is 90% unionized; thus, alfentanil's diffusible proportion is higher than that of other synthetic opioids like fentanyl and time to onset of action is very short. In the liver alfentanil is processed by several metabolic routes: dealkylation, demethylation, hydroxylation, and also glucuronide conjugation, and all these end-product are free from clinical analgesic activity. Hepatic degradation involves cytochrome P450 3A4/3 and CYP 3A5; these isoforms largely vary in activity in humans because of pharmacogenetics, and this accounts for the broad clinical effect among patients and drug interactions.

### 6.3.4 Sufentanil

After a single IV bolus, sufentanil is largely taken up in lung tissue, similar to fentanyl; with a  $pK_a$  of 8.0, the same as morphine, in plasma pH is almost totally in the ionized form (80%). It is highly bound to plasma proteins, mainly albumin and  $\alpha_1$ -acid glycoprotein, and is very highly lipid soluble. Sufentanil is dealkylated, hydroxylated, and demethylated in the liver.

Sufentanil is 5–10 times more potent as an analgesic than fentanyl. Its great hemodynamic stability and the limited clinical relevance of histamine release make it the opioid agent of choice for cardiovascular surgery. Moreover, its half-life after prolonged infusion is not as long as that of fentanyl. Taking these aspects into account, sufentanil should be considered a practical and appropriate analgesic option for use in selected cases in the ICU [35].

### 6.3.5 Remifentanil

Remifentanil is chemically similar to fentanyl congeners but with an ester linkage that distinguishes it, in term of PK, from all other opioids. Ester linkage allows it to be metabolized by hydrolysis from ubiquitous nonspecific esterases, with very rapid degradation to inactive products and plasma concentration breakdown after the end of infusion, even in the case of very long and continuous administration. This also means that clinical infusion must be continuous.

Its widespread and extrahepatic metabolism is suggested by the its very rapid clearance, which is several times higher than the hepatic blood flow [50]. It is not sequestered or degraded in the lungs; it performs like a weak base, with a  $pK$  of 7.07. It is highly lipid soluble and highly protein bound to plasma protein (mainly  $\alpha_1$ -glyco protein).



The onset time after continuous infusion has started is within 1 min and it rapidly achieves a steady-state plasma concentration; action offset is rapid, in 3–10 min, and context-sensitive half-life is 3–4 min, even in the case of very long continuous infusions [51–53].

De-esterification from nonspecific esterases forms a carboxylic acid that is very poorly, and clinically irrelevant, active as an opioid. It is excreted by renal function but even in case of severe renal impairment there is no relevant risk of adverse side effects. In clinical terms, remifentanyl's degradation and metabolism are not affected by hepatic and/or renal function; esterases from red blood cells are mainly responsible for degradation; pseudocholinesterases are not active in remifentanyl.

Remifentanyl is mainly bound to the  $\mu$  receptor; its major features comes from its metabolism, which is not affected by organ failure, and very rapid onset and offset times, so that it is the opioid agent of choice in cases of severe hepatic and/or renal failure, even in the case of prolonged infusions, without any effect on time of weaning from mechanical ventilation [54, 55]. Moreover, its metabolism is not affected drug interactions, making it very easy to predict onset and offset times; the properties of organ-independent metabolism, lack of accumulation, and precision and predictability of clinical effect make remifentanyl a promising agent, alone or in combination with a sedative agent, in analgesia-based sedation in ventilated ICU patients [35]. As with other opioid agents, side effect such as bradycardia, hypotension, muscle rigidity, and nausea can occur with remifentanyl. Of note, remifentanyl's preparations contain glycine and should not be given via neuraxial routes. Dosing should be based on ideal body weight in obese patients.

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## 6.4 Dexmedetomidine

Dexmedetomidine is a selective  $\alpha_2$ -receptor agonist, with an  $\alpha_2/\alpha_1$  binding affinity ratio of 1620:1; with eight times more affinity to  $\alpha_2$  receptors than clonidine [56]. This drug has a favorable pharmacologic profile owing to its sympatholytic, sedative, analgesic (opioid-sparing), and anxiolytic, and anesthetic drug-sparing effects and, of note, without respiratory depression [57]. Dexmedetomidine, an  $\alpha_2$ -adrenergic agonist, acts by binding to G-protein-coupled  $\alpha_2$  adrenergic receptors, which are found in the central, peripheral, and autonomic nervous systems and in various vital organs and blood vessels throughout the body [58]. There are three subtypes of these receptors, namely  $\alpha_2A$ ,  $\alpha_2B$ , and  $\alpha_2C$ , each having different functions and activities. Agonism at the  $\alpha_2A$  receptors appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection, and inhibition of insulin secretion; agonism at the  $\alpha_2B$  receptors suppresses shivering centrally, promotes analgesia at spinal cord sites, and induces vasoconstriction in peripheral arteries. The  $\alpha_2C$  receptor is associated with modulation of cognition, sensory processing, mood- and stimulant-induced locomotor activity, and regulation of adrenalin outflow from the adrenal medulla, whereas inhibition of noradrenalin release appears to be equally affected by all three  $\alpha_2$  receptor subtypes [59]. Dexmedetomidine is considered to have more affinity for  $\alpha_2A$  and  $\alpha_2C$  receptors as compared to clonidine [60].

Dexmedetomidine has a very high first-pass metabolism so that it has poor bioavailability [61]. It is rapidly distributed with a high volume of distribution (Vd 1.33 L/kg) and an elimination half-life of 2.0–2.5 h. Highly protein bound (6% free fraction), it does not displace other protein-bound agents commonly used in anesthesia care. After IV injection, dexmedetomidine has an onset of action after around 15 min and peak concentrations are commonly reached in an hour after continuous infusion, without any bolus injection, has started. Rapidly distributed away from the site of action (central nervous system), it has a half-life of 6 min and an elimination half-life of approximately 2 h [59]. Context-sensitive half-life varies with the extent of the infusion, from 4 min for a very short time administration, up to 250 min for an 8-h infusion. These pharmacokinetic properties permit easy dose titration in response to fluctuating sedative needs [35]. Metabolized in the liver, with a cytochrome P-450-mediated phase 1 activation of hydroxylation and subsequent glucuronidation to form an inactive metabolite that is excreted in the urine and only in a small amount in feces. The dose should be cautiously adjusted and tailored in patients with hepatic failure because of diminished metabolism.

Dexmedetomidine provides dose-dependent increases in anxiolysis and sedation [59]. Sedative effects are due to hyperpolarization of noradrenergic neurons in locus coeruleus, thus inhibiting noradrenaline release with the final effect of reducing and inhibiting activity in descending medullospinal noradrenergic outflow [62, 63]. Sedation from dexmedetomidine, in comparison to other GABAergic agents, is different; arousability is maintained even at a very deep level of sedation and a very good correlation between sedation assessment scales and EEG analysis methods has been demonstrated [64]. This kind of sedation is called “cooperative sedation” and allows patients to cooperate during ICU nursing and radiologic, airway, and neurosurgery procedures [65, 66]. Of note, arousability without any need for withdrawal of infusion allows daily assessment for mechanical ventilation discontinuation and potentially shortens the weaning process. Sedation from dexmedetomidine has respiratory pattern and EEG changes similar to natural sleep (see the dedicated Chap. 11) [67].

Dexmedetomidine has analgesic properties, probably not primarily but mainly detected through an opioid- and propofol-sparing effect instead [68, 69]; this effect is mediated by  $\alpha_2C$  and  $\alpha_2A$  receptors on neurons of superficial dorsal horn in lamina II that act to inhibit the release of nociceptive transmitters—substance P and glutamate—and by hyperpolarization of spinal interneurons, modulating the afferent inlet [70]. Some studies advocate that a reduction of the affective motivational component of pain could play a role in the analgesic clinical effect of dexmedetomidine [71]. Finally, it could act locally, as suggested by the evidence of analgesic action of dexmedetomidine administered intra-articularly for knee surgery, probably through agonism on local  $\alpha_2A$  receptors [72, 73].

Dexmedetomidine causes dose-dependent decreases in heart rate and blood pressure, concomitant with decreasing plasma catecholamines [59]. After a high-dose bolus, the clinical effect on hemodynamic conditions is biphasic, with an initial transient rise in arterial pressure and a reflex fall in heart rate, due to stimulation of  $\alpha_2B$  subtypes of receptors present in vascular smooth muscles. Subsequently, arterial pressure and heart rate decrease due to inhibition of central sympathetic outflow and stimulation of pre-synaptic  $\alpha_2$  receptors causing a decrease of noradrenaline release,

leading to a further decrease in blood pressure [74, 75]. These effects are clinically relevant in those patients in whom hemodynamic conditions rely on augmented sympathetic stimulation and vasoconstriction, e.g., those with fixed stroke volume and hypovolemic status, on rate-reducing drugs (beta blockers or digitalis).

Dexmedetomidine causes a reduction in cerebral blood flow and cerebral metabolic demand of oxygen with a slight reduction in intracranial pressure. It has been found to have neuroprotective effects by reducing circulating and cerebral catecholamines. Neuroprotection comes from a reduction of excitotoxicity and improvement of blood supply to the ischemic cerebral tissues. It also reduces the levels of glutamate, which is found to enhance cellular brain injury especially in subarachnoid hemorrhage [65].

The great clinical value and utility of dexmedetomidine are due to a minimal decrease in the minute ventilation even at values 15 times higher than normal plasma levels [76]. The decrease in minute ventilation may produce a mild hypercapnia, which is clinically irrelevant, without affecting pH, arterial, or the carbon dioxide ventilatory response curve [67, 77]. As a result, compared with remifentanyl, the hypercapnic arousal is preserved and the apnea threshold is actually decreased [67].

Due to the possibility to obtaining so-called “cooperative sedation,” it has been successfully used in processes of tracheal extubation and beyond for those patients in whom prior attempts failed because of excessive agitation [78, 79], and with similar results for those patients requiring non-invasive ventilation [80]. This feature allows dexmedetomidine to be considered a very useful agent for weaning patients from mechanical ventilation who still require light sedation [35]. Of note, it has been used to perform fiberoptic intubation or other difficult airways procedures, taking further advantage of the decrease in saliva production and airway secretions [81].

Dexmedetomidine's clinical effects also include decreased salivation, increased glomerular filtration rate, decreased intraocular pressure, decreased shivering threshold, decreased bowel motility, and decreased insulin release from the pancreas [82]. Shivering suppression, like other  $\alpha_2$  agonists, possibly acts through  $\alpha_2B$  receptor agonism in the hypothalamic thermoregulatory center of the brain [83].

Several side effects have been reported, the most common of which are hypertension, hypotension, and bradycardia, and could be avoided, omitting the loading dose or slowly increasing the infusion rate [84]. Less common side effects reported include dry mouth, nausea, vomiting, chills, fever, pleural effusion, pulmonary edema, etc. [85].

Long-term infusions of dexmedetomidine may result in up-regulation of receptors leading to the development of a withdrawal syndrome on abrupt discontinuation manifesting as nervousness, agitation, headaches, and hypertensive crisis. On the other hand,  $\alpha_2$ -adrenergic agonists such as clonidine have a role in the treatment of central hyperadrenergic state arising from drug withdrawal (opioids, alcohol, or cocaine) due to their effect on sympathetic outflow decrease [59].

An absolute contraindication to dexmedetomidine is represented by hypersensitivity; in patients with hepatic impairment a dose reduction may be considered, caution must be exercised in patients with hypovolemia, diabetes mellitus, chronic hypertension, advanced heart block, and the elderly, in whom hypotension and bradycardia may be more pronounced. Dexmedetomidine blunts the sympathetic response in patients who depend on a high level of sympathetic tone or have reduced myocardial function [58, 86] (Table 6.5).

**Table 6.5** Physicochemical characteristics and pharmacokinetics of common drugs for sedation in adults

Drug	Propofol	Dexmedetomidine	Midazolam	Droperidol
pKa	11.1	7.1	6.0	7.5
Plasma binding (%)	98	94	94–98	–
Metabolism	Hepatic metabolism; (glucuronidation). Having an extrahepatic metabolism (lung and renal). No active metabolite	Glucuronidation and cytochrome P450-mediated metabolism. Not affect by renal impairment	CYP3A4 and CYP3A5 Metabolite with similar sedative activities profound sedation in renal impairment	Hepatic metabolism
Elimination half-life (h)	4–7	2–3	1.7–2.6	1.7–2.2
Clearance (ml/kg/min)	20–30	20–30	6.4–11	14
Sedation dose ev	25–75 µg/kg/min	0.1–1 µg/kg/h	0.5–1 mg repeated, 0.07 mg/kg IM	–
Induction	1–2.5 mg/kg reduced with age	–	0.06–0.15 mg/kg	–
Maintenance	50–150 µg/kg/min in combination with opioid	–	0.05 mg/kg pm	–
CSHT <sup>a</sup>	For infusions of up to 8 h is less than 40 min	From 4 min after a 10-min infusion to 250 min after an 8-h infusion	More than 60 min after a 3-h infusion	
Effect on				
HR	=/↓	=/↓	=	
MBP	↓	=	=/↓	
RR	↓ ↓ apnea	=	=	
Comment	Also have an antiemetic action	Provide analgesia Attention in Child-Pugh class A, B, or C clearance may be slower	Affected by obesity, age, and hepatic cirrhosis	Potential for fatal arrhythmias Antiemetic use

<sup>a</sup>Context-sensitive half-life

## 6.5 Propofol

Propofol is the most frequently used IV anesthetic today [31]. Work in the early 1970s on substituted derivatives of phenol with hypnotic properties resulted in the development of 2,6-diisopropylphenol (propofol), and in 1977 it was described as a potential agent to induce anesthesia [87]. Insoluble in water, propofol was first formulated with Cremophor EL (BASF A.G.), but several anaphylactoid reactions were described successively so that it was then prepared as an oil in water emulsion. The formulation that followed the removal of Cremophor consists of 1% propofol in

water, 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide; it provides 1.1 kcal/ml from fat and should be counted as a caloric source. Reports of infections in patients receiving propofol prompted the addition of 0.005% ethylenediaminetetraacetic acid (EDTA) to retard bacterial growth [35]. This formulation has a pH of 7 and the appearance of a slightly viscous, milky white substance. In Europe, a 2% formulation and a formulation in which the emulsion contains a mixture of medium-chain and long-chain triglycerides also are available [31]. Caregivers should adhere to a strict aseptic technique and administer propofol through a dedicated IV line to avoid drug incompatibility problems. Introduced in clinical armamentarium in 1982 as an induction agent for general anesthesia, over the past decades propofol has been identified as an agent that is indicated for induction and maintenance of anesthesia and sedation in and outside the operating room and ICU. It has anxiolytic/sedative/hypnotic, antiemetic, antipruritic, anticonvulsant, bronchodilatory, muscle relaxant, and possibly anti-inflammatory and antiplatelet effects [35, 88]. Propofol's amnestic properties are similar to that of the benzodiazepines [89, 90].

The lipophilic properties of propofol allow it to easily cross the blood-brain barrier rapidly and it has a rapid onset of action (1–2 min) and a short duration of action (10–15 min after a single-dose administration or a short infusion); for patients given infusions for longer than 72 h, the wake-up time can be extended to 60 min [35, 91]. More precisely, it has been shown that the offset of action of propofol can vary considerably and is a function of the depth of sedation, duration of the infusion, patient size, age, and body composition, and emergence from a deep sedation for a long period can last for up to 3 days [92].

Pharmacokinetic properties are best described by a three-compartment model where, after a single bolus, it rapidly crosses the blood-brain barrier to the effector site to then redistribute to less perfused tissue (rapid onset/offset of action). It has an elimination half-life span from 30 to 60 min; it is metabolized in the liver through conjugation to glucuronide and sulfate to form water-soluble inactive products, and is then eliminated in the urine. Propofol has a large volume of distribution of 600–800 L, suggesting that the drug is rapidly cleared from the central compartment into fatty tissues, and elimination is not appreciably altered by hepatic or renal failure [35]. Because clearance of propofol exceeds hepatic blood flow, extrahepatic metabolism or extrarenal elimination has been suggested. Extrahepatic metabolism has been confirmed during the anhepatic phase of patients receiving a transplanted liver [31]. In two more recent studies, the role of the kidneys in propofol metabolism was established, accounting for 30% of total body clearance [93, 94]; the lungs also may play an important role in this extrahepatic metabolism and they are responsible for approximately 30% of the uptake and first-pass elimination after a bolus dose [95]. Its rapid onset and offset of action provide clinician with a sedative option that is far more titratable than that of benzodiazepines; an IV infusion of propofol can be predictably titrated from light sedation to a deeper hypnotic state for patients who require varying levels of sedation throughout the day. Simply stopping the infusion can reverse the sedative effects, usually within 1 h and often within 15 min. Propofol is considered the preferred sedative agent for patients in whom rapid awakening is important [3].

Hepatic or renal disease does not appear to affect clearance from propofol, although in critically ill patients, probably because of reduced hepatic perfusion, clearance is slower [22]; at the same time, a study from Peeters et al. found that patients who are sicker (based on a SOFA score) are more likely to have a deeper level of sedation that may be related to decreased propofol clearance [96]. Elderly patients have decreased clearance and thus maintenance infusions should generally be reduced in an age-related fashion [89].

Propofol acts as a hypnotic agent by enhancing  $\gamma$ -aminobutyric acid (GABA)-induced chloride current coming after its binding to the  $\beta$ -subunit of GABA receptor [31]. Propofol, through its action on GABA receptors in the hippocampus, inhibits acetylcholine release in the hippocampus and prefrontal cortex, but it seems to also play a role in the case of the  $\alpha$ 2-adrenoreceptor system and in inhibition of the NMDA subtype of glutamate receptor [97–99]. In contrast to barbiturates, propofol is not analgesic. Of note, propofol has a potent antiemetic action, probably thanks to a decrease in serotonin levels observed in the area postrema through its action on GABA receptors [100]. Propofol increases dopamine concentrations in the nucleus accumbens, a phenomenon noted with drugs of abuse that may explain the sense of well-being reported by many patients [101, 102].

Largely used to sedate brain trauma patients, propofol decreases intracranial pressure (ICP) in patients with either normal or increased ICP by a percentage of 50%, but this decrease is associated with a significant drop in mean arterial pressure and thus of cerebral perfusion pressure [103]. For this reason, propofol in head-injured critically ill patients should be limited to providing mild to moderate sedation [104]. When used to provide anesthesia during neurosurgical procedures, propofol has a lower vasodilatory effect than volatile anesthetics have. Normal cerebral reactivity to carbon dioxide and autoregulation are maintained during propofol infusion [105].

The effect of propofol on epilepsy manifestations is controversial. Propofol-related seizures have been described, mainly on induction or emergence from anesthesia, but at the opposite end, a direct and dose-dependent anticonvulsant effect has been shown, and it has been used to treat epileptic seizures [106–108]. There have been a few reports of convulsions after propofol administration even though the incidence is rare (1 in 50,000 administrations). On somatosensory-evoked potentials propofol causes a decrease in amplitude of the early components with a small increase in latency of late components [109]; it does not alter brainstem auditory-evoked potentials [110]. Many anesthetic-related drugs decrease the required dose or blood concentrations of propofol's pharmacologic action [31]; co-administration of an opioid or of a volatile anesthetic significantly reduces concentrations needed to suppress awakening to verbal stimuli or motor response to surgical incision and recall [111–113].

After an induction dose of Propofol, apnea usually occurs, depending on the dose, speed of administration, and other premedication [114]; the addition of an opioid may prolong apnea beyond 30 s, even though it has been injected as a premedication agent [114, 115]. Propofol is a respiratory depressant even in the case of continuous infusion: a maintenance infusion of propofol (100  $\mu$ g/kg/min) results in

a 40% decrease in tidal volume and a 20% increase in respiratory frequency, with an unpredictable change in minute ventilation; the drive response to carbon dioxide is also decreased [115]. Continuous infusion of propofol also depresses ventilator response to hypoxia, presumably by a direct action on carotid body chemoreceptors [116]. On chronic obstructive pulmonary disease-affected patients, propofol induces bronchodilation and it attenuates vagal bronchoconstriction presumably through a direct action on muscarinic receptors [117, 118].

Propofol has negative inotropic effects and can cause vasodilation and dose-related hypotension. Patients should be euvoletic before a slow bolus or infusion is administered [35]. During induction of anesthesia a decrease in arterial blood pressure is a common side effect; it is independent of cardiovascular coexisting conditions and a 25–40% reduction of systolic blood pressure is usually seen [119–121]. The decrease in arterial pressure is associated with a decrease in cardiac output/cardiac index ( $\pm 15\%$ ) [120, 121], stroke volume index ( $\pm 20\%$ ) [121], and systemic vascular resistance (15–25%) [120]. Left ventricular contractility indexes, such as  $dP/dt$ , are also decreased after an induction dose [31]. Focusing on right ventricular function, propofol produces a marked reduction in the slope of the right ventricular end-systolic pressure-volume relationship [122]. Although the decrease in systemic pressure is due mainly to vasodilation, the direct decrease of myocardial contractility is more controversial and probably acts through a direct effect on sympathetic drive to heart. Clinically, the hemodynamic conditions alter in a dose-dependent fashion [123]. The reduction in sympathetic activity produces vasodilation via a direct effect on intracellular smooth muscle calcium mobilization [124], inhibition of prostacyclin synthesis in endothelial cells [125], reduction in angiotensin II-elicited calcium entry [126] and activation of  $K^+$  adenosine triphosphate channels, and stimulation of nitric oxide. Heart rate, after a single induction dose, is not significantly affected; propofol may diminish the baroreflex to hypotension and the response to atropine [127]. Clinically, risk factors for hypotension after anesthesia induction with propofol are American Society of Anesthesiologists (ASA) class II through V, baseline mean arterial pressure less than 70 mmHg, age 50 years or older, and co-administration of fentanyl [128]. Because the vasodilatory and myocardial depressant effects are concentration-dependent, and given that concentrations achieved with induction doses are largely higher than those from continuous infusion, the decrease in arterial blood pressure from propofol during the infusion phase (maintenance of anesthesia) is much less than that seen after an induction of anesthesia bolus [31]. An infusion of propofol results in a significant reduction in myocardial blood flow and myocardial oxygen consumption, a finding that suggests that the global myocardial oxygen supply-to-demand ratio is preserved [119, 129]. During maintenance of anesthesia or sedation, heart rate may be unaffected or increase/decrease: in the single patient case, probably a role is played by the patient's condition, concomitant drugs administered, and the extent, if present, of hypotension [129–131].

Propofol, even if given at subhypnotic doses, exerts a significant antiemetic action and has been successfully used at very small bolus doses of 10 mg to treat postoperative nausea and vomiting (PONV) [132]; during breast surgery, anesthesia



maintenance with propofol has been showed to be superior to ondansetron 4 mg in preventing PONV [133]; it has been used as a subhypnotic continuous infusion (1 mg/kg/h) to manage post anticancer chemotherapy nausea and vomiting [31]. At the same doses, propofol is as active as naloxone against pruritus triggered by spinal opioids [134] or cholestatic pruritus.

Continuous infusions, especially at high rates, can cause hypertriglyceridemia; patients who are older and have a longer ICU stay are at major risk of this occurrence, which can be further complicated by the development of pancreatitis [135]. In the case of a high rate and long duration of infusion, serum triglyceride concentrations should be monitored [136].

Described first in children, propofol infusion syndrome (PRIS) is an acute, rare, and often life-threatening condition characterized by acute refractory bradycardia progressing to asystole and one or more of: metabolic acidosis (base excess > 10 mmol/L), rhabdomyolysis of both skeletal and cardiac muscle, hyperlipidemia, enlarged or fatty liver [137]. Although the underlying pathophysiological mechanism is still not completely elucidated it has been observed that, in the setting of long periods of glucose deficiency, when cellular metabolism depends on fatty acids, propofol can uncouple the mitochondrial respiratory chain in heart and muscle cells [138–140]. PRIS has been described as an “all or none” syndrome without a degree of symptoms; common signs and symptoms associated are lactic acidosis, arrhythmia, hypotension, multiorgan failure, acute renal failure, rhabdomyolysis, and elevated serum creatine kinase, serum urea, and serum potassium, lipemic plasma, liver enlargement with increased liver enzymes and green- or red-colored urine [141].

Risk factors for PRIS, identified from case reports, are: airways infection, severe head injury, neurologic or inflammatory illness, high-dose propofol sedation over 48 h at over 4–5 mg/kg/h, increased catecholamine and glucocorticoid serum levels, and low energy supply [142]. Children are more prone to the development of PRIS due to low glycogen storage and high dependence on fat metabolism [143]. Fat overload associated with propofol infusion may also contribute to increased plasma fatty acids [144].

Caution should be exercised when propofol is infused for more than 48 h at dosages above 5 mg/kg/h, particularly in patients with neurologic or inflammatory illnesses [145] and in every patient who develops unexplained metabolic acidosis or cardiac arrhythmias. The US Food and Drug Administration (FDA) suggest considering an alternative agent when a deeper level (or longer period) of sedation is required in pediatric patients and in adults who require vasopressors or cardiac inotropes [3].

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## 6.6 Benzodiazepines

Benzodiazepines are among the most often administered classes of agents in critically ill patients, not only to achieve a state of deep sedation and amnesia but even in the case of a need for an anxiolytic effect [146]. This wide range of clinical



effects depends on the proportion of GABA receptors interacting with benzodiazepines: anxiolysis is seen when 20% of GABA receptor sites are bound; 30–50% interaction cause sedation whereas hypnosis occurs with at least 60% of available sites bound to benzodiazepines [147]. These agents induce antegrade amnesia; they show an opioid-sparing effect thanks to the action on the anxious component of pain [148]. Benzodiazepines also exhibit anticonvulsant and muscle relaxant effects that may be desirable in selected ICU patients. They also show a clinically relevant respiratory depression that is more evident in the case of medication with opioids or other hypnotic agents [146]. In recent years, even greater evidence is emerging that delirium among critically ill patients is related to the administration of benzodiazepines and hypnotic/sedative agents at infusion rates able to induce so-called “over sedation” [2]. Strategies aimed at reducing the administration of benzodiazepines could help to reduce the incidence and severity of delirium and potentially of all the consequences in terms of clinical outcome worsening [2, 149]. Nonetheless, when not promptly detected, hyperactive delirium state, usually lead to improper sedative prescription with a potential iatrogenic worsening of clinical conditions [150]. Delirium is associated with increased mortality in adult ICU patients, with prolonged ICU and hospital length of stay in adult ICU patients and with the development of post-ICU cognitive impairment [2]. Concerns about delirium and its consequences have made benzodiazepine usage less popular for delivering critical care sedation in the last years.

Pharmacodynamics: the wide range of clinical effects of benzodiazepines are mediated through GABA<sub>A</sub> binding sites on neuronal GABA receptors. After their interaction, benzodiazepines facilitate chloride conductance through the GABA receptor, with subsequent membrane hyperpolarization and inhibition of neuronal impulses [151]. Flumazenil is a somewhat different benzodiazepine that acts as an antagonist or inverse agonist [151].

Midazolam is a short-acting, water-soluble benzodiazepine; in the bloodstream, at physiologic pH, it converts into a lipid-soluble form whereby closure of the diazepine ring turns it into a lipid-soluble molecule that rapidly crosses the blood-brain barrier to enter the CNS to produce sedation in 2–5 min. The agents, after a single bolus, rapidly offset the clinical effect by redistribution to peripheral tissues, where it is stored in adipose tissue. It undergoes extensive oxidation in the liver via the P450 cytochrome enzyme system to form a water-soluble compound, hydroxymidazolam glucuronide, excreted by the kidneys [23]; this compound has CNS depressant effects, 10% of potency of the parent drug, and may accumulate in the case of renal impairment. The mean elimination half-life is around 10 h but in the case of continuous infusion for sedation it may increase to 30 h as it is released from adipose tissue. Many of the usually prescribed agents in critically ill patients act as inhibitors of CYP3A4, such as macrolide antibiotics, diltiazem, propofol, and fluconazole; they may reduce the metabolism of midazolam and prolong its sedative actions [152]. These many potential interactions bring about diminished protein binding availability, fluid shifts and tissue edema, impaired organ function, and can translate into an unpredictably prolonged offset of action time, with an unacceptable awakening time after continuous infusion discontinuation. For these reasons, the

2013 Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit suggest a non-benzodiazepine agent for sedation in critically ill patients because of its role on prolonging ICU length of stay [2].

Unlike midazolam, lorazepam undergoes hepatic glucuronidation to an end-metabolite that lacks any clinical effects; this feature, together with PK that is not altered by age, let to better predict awakening time after continuous infusion discontinuation, and 2002 Practice Guidelines recommended lorazepam over midazolam in the case of long-term sedation. Among the injectable benzodiazepines, lorazepam is the least lipophilic and it slowly enters the CNS, with a resulting slow onset time of action (5–20 min); elimination half-life is 10–20 h [151], but it can take longer in the case of severe renal and/or hepatic impairment and after chronic sedation. Concerns have been raised for polyethylene glycol (PEG) and propylene glycol (PG) toxicity from lorazepam infusion; these compounds are used to facilitate drug solubility and they can accumulate in the case of a very high infusion rate for prolonged periods; their toxicity has been associated with the development of severe lactic acidosis, hyperosmolar coma, and nephrotoxicity [153–155]. In addition to long-term and high-dose lorazepam infusions, other identified risk factors for PEG/PG toxicity include renal and hepatic impairment, pregnancy, young age and concomitant therapy with metronidazole [146]. A serum osmolar gap increase is the first sign detected in the case of toxicity development [156], and discontinuing lorazepam infusion is usually sufficient to correct the situation; hemodialysis should be reserved for severe cases [157].

Diazepam is highly lipophilic and this feature allows rapid distribution to the CNS and a short onset of action (2–5 min) after a single IV bolus. Diazepam has a high volume of distribution in critically ill patients, averaging 2.9 L/kg; highly protein bound and metabolized by cytochrome CYP450 microsomal enzymes to the active metabolites, oxazepam and desmethyldiazepam. The mean half-life of diazepam is 72 h, but there is wide interpatient variability and unpredictability. Oxazepam has a half-life of 10 h and undergoes further conjugation in the liver before elimination. Desmethyldiazepam has a half-life between 100 and 200 h and is eliminated by the kidneys; therefore, sedative effects may be prolonged in patients with moderate to severe renal and or hepatic failure [151]. Wide variability on diazepam metabolism comes from genetic polymorphism of the CYP450 enzyme system, more precisely on CYP2C19. Some of its isoenzymes, which are present in 3–5% of Caucasians and African Americans and 12–100% of Asian ethnic groups, are associated with a significant decrease in diazepam metabolism. Clinically speaking, it may imply that a patient treated with diazepam may experience unexpectedly prolonged sedation [158]. Moreover, the CYP2C19 isoenzyme can be affected by several medications, inhibited by amiodarone, fluconazole, omeprazole, valproic acid, but even induced by cigarette smoking [159]. For these reasons, the clinical response to diazepam is often unpredictable in critically ill patients.

Benzodiazepines can cause hypotension due to vasodilation or respiratory depression when given in large amounts, so that in patients whose airways are not secured, they should be given cautiously [146]. These effects are clinically more evident in the case of administration with opioids. If these effects need to be rapidly

reversed, flumazenil may be used to rapidly antagonize benzodiazepine effects, almost immediately; it should be administered IV in doses of 0.2–1 mg. Caution must be exercised with regard to the PK properties of flumazenil: it is metabolized rapidly, with a half-life of 1 h but with a clinical duration of effect of often less than 30 min; thus, in case of need for prolonged reversal, a continuous flumazenil infusion should be initiated. Flumazenil is relatively contraindicated in patients with known benzodiazepine dependence and chronic use, because acute withdrawal symptoms and seizures have been reported in these patients [152].

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## 6.7 Barbiturates

Thiopentone is a short-acting barbiturate that has anesthetic, anticonvulsant, and cerebro-protective properties and induces hypnosis within 30–40 s after IV induction with a dose of 3–5 mg/kg. Barbiturates have previously played a central role in the sedation of patients in the ICU, especially those with traumatic brain injury [160]. In 2012 a Cochrane review concluded that there was no evidence that barbiturates improve outcome in patients with traumatic brain injury as their administration may result in a fall in blood pressure and in cerebral perfusion pressure in up to 25% of patients [161]. Nowadays the use of thiopentone is limited to continuous infusion in the management of refractory status epilepticus and reduction of refractory intracranial hypertension [162].

Barbiturates are formulated as sodium salts and they have to be reconstituted with water, glucose 5%, or normal saline, not with an acid solution that can result in precipitation of free acids (i.e., not coadministered with atracurium, rocuronium, sufentanil, dobutamine, and midazolam) [163]. Barbiturates bind to a specific site of GABA $\alpha$  receptor; at low dose they enhance the effects of GABA mediator, and at high doses they directly activate GABA $\alpha$  receptors producing dose-dependent sedation and general anesthesia. Thiopentone has a high lipid solubility that allows a rapid blood-brain barrier crossing, with a resultant fast onset of action; it is metabolized in the liver and shows a very low clearance rate and after continuous infusion the hepatic enzymatic system is saturated and its metabolism may become linear [164]. Potential adverse effects are hypotension, gastroparesis, loss of thermoregulation, immunosuppression, myocardial depression, bronchospasm, angioedema, cough, laryngospasm, loss of airway reflexes, and respiratory depression. For these reasons it is now clinically limited to those indications above mentioned.

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### Conclusions

The proper use of intravenous sedation in the ICU holds promise for patient comfort as well as decreased morbidity and mortality.

There are now very potent analgesic and sedative drugs available that have minor side effects and practitioners should become experts in administration of these drugs and should understand the concepts related to different methods of administration. Much safer treatment can be achieved if we pay greater attention to drug administration and to their pharmacologic actions. While PK differences

have been described in various populations, the clinical effects and adverse outcomes are greatly influenced by numerous independent physiologic alterations seen in critical care patients. In particular, patients with severe alterations in liver and renal function must be treated judiciously because of being predisposed to metabolic disarray. Appropriate selection of the drug, titration of doses to clinical effects, and careful patient assessment and monitoring, are crucial for achieving desired therapeutic outcomes with IV sedative agents in ICU.

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# Volatile Anesthetics for Intensive Care Unit Sedation

# 7

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## 7.1 Volatile Anesthetic Agents

Volatile agents (VAs) for anesthesia have more than a century-long history [1]. Modern inhalational anesthetics consist of the halogenated (fluorinated) ether derivatives isoflurane, desflurane, and sevoflurane [2]. By virtue of their structure, these small hydrocarbons possess the unique ability to be massively and rapidly absorbed with breathing, showing fast action (onset and offset), minimal accumulation, low metabolism, and negligible tachyphylaxis or tolerance [3]. These favorable pharmacokinetic properties made them particularly suitable for use in the fast-paced environment of the operating room, as they permit fast emergence from anesthesia with an adequacy of sedation and immobility comparable to all other agents [4, 5].

The mechanism of action of volatile anesthetic agents is highly pleiotropic. A comprehensive theory of the molecular action of these fluorinated hydrocarbons is still immature, albeit a clear influence on many receptors known to impact sedation/consciousness, pain processing, immobility, and amnesia has been demonstrated [6].

Given these beneficial features, do volatile anesthetics have space outside the operating room as main sedatives? Can technical, safety, and efficacy problems be solved? These questions have been investigated for more than 15 years [7].

This chapter will focus on the current state of the art of inhaled anesthetics for sedation in the intensive care unit (ICU). It will initially focus on how these agents can be properly delivered via modern devices and scavenged without risk for ICU personnel and for the environment. After this it will explore what the advantages of these agents are when used for sedation in the critically ill and what other properties aside from sedation may be beneficial to the acute patient. Following this, it will analyze the intrinsic limitations connected to volatile anesthetic use compared to the

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particular needs of a critical care population. Finally, it will discuss VA use for treatment of specific illnesses like status asthmaticus and severe epilepsy, as well as support for acute respiratory distress syndrome (ARDS).

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## **7.2 Technical Features of Volatile Anesthetic Use in the Intensive Care Unit**

Volatile anesthetics, isoflurane above all, were reportedly used in the ICU since the end of the 1980s. The first administration strategies used conventional ventilators and vaporizers, subsequently exchanged with more practical closed-circuit systems [8, 9]. Difficulties with the early use of VAs in the ICU were numerous, particularly because equipment was costly and impractical for use in such environment. Cost and ambient pollution, as well as possible toxicity for healthcare workers and pregnant bystanders, were prominent issues and are investigated in volatile sedation studies even nowadays.

### **7.2.1 The Anesthetic Conserving Device System (AnaConDa™)**

The anesthetic conserving device (ACD—the first being AnaConDa™, Sedana Medical, Uppsala, Sweden) was developed in 1999 and officially presented in 2004. It showed a striking advantage: it made it possible to safely and practically administer volatile anesthetics with any common intensive care ventilator [10].

This was achieved via a revolutionary piece of technology: the reflector filter. The principle of this device is to absorb the anesthetic exhaled by the patient and readminister up to 90% of the absorbed dose with the next breath. The ACD is a modified heat and moisture exchanger (HME), a section of the breathing piece capable of conserving heat and humidity coming from the patient into the otherwise cold dry breathing system of common ventilators, equipped with activated charcoal fibers able to store the inhaled anesthetic [11, 12]. The ACD is positioned between the Y-piece of the circuit and the patient, just as a bacterial filter, adding a dead space of 100 mL. The liquid anesthetic agent is infused via a syringe pump and converted through a porous evaporator rod on the patient's side of the breathing piece to a breathable vapor. Thus constructed, its efficiency corresponds to a circle system with a fresh gas flow of 1.5 L/min (to bear in mind for dose adjustment) with no need for CO<sub>2</sub> absorption which is exhaled normally [13, 14]. This is true as long as the reflector capacity (up to 10 mL for each expired breath) is not exceeded [15]. So if a 0.5% dose of anesthetic agent is to be rebreathed, the tidal volume has to be around 500 mL, and infusion rates have to be increased or reduced with increases or reductions of minute ventilation, respectively, to maintain the end-tidal concentrations of anesthetic stable.

The device is disposable and can be used with either isoflurane or sevoflurane. The liquid anesthetic is transferred from the bottle to a device-specific 50 mL syringe via a dedicated adaptor (other syringes must not be used, as the anesthetic

can dissolve the plastic material releasing toxic products [14]) and then administered via a rubber supply line, driven by any common syringe pump. Infusion rates should start at 5–10 mL/h while allowing the gas sample port to detect end-tidal concentrations of the chosen agent; after that the physician can titrate the infusion rate on the basis of the minimum alveolar concentration (MAC; this, together with the end-tidal percent concentration, is shown on the device display). Sedation should be achieved at end-tidal concentrations corresponding to roughly half to one-third of the MAC of the anesthetic (i.e., circa the MAC-awake concentration) [13], that is, rates of 2–5 mL/h (0.3–0.5 expired vol%) for isoflurane and 2–6 mL/h (0.5–1 expired vol%) for sevoflurane.

An external gas monitor is required to measure anesthetic gas concentration, usually via the sidestream sample mechanism. The system measures the peak vapor concentration at the onset of actual inspiration when, by action of the sum of the injected anesthetic and the “reflected” dose, the percent amount is maximal. This is the calculated end-expiratory concentration ( $F_{et}$ ) and an estimate of brain concentration. The system does the same to calculate end-tidal carbon dioxide concentration and plot the capnographic curve [14].

The system must be used in respect to some caveats. The single-use parts must be changed every 24 h for hygienic reasons. The presence of air bubbles in the syringe must not be tolerated as the anesthetic may evaporate into them and expand them [13]. Fluorinated hydrocarbons are very dense, so caution must be kept not to elevate the syringe above the patient to avoid the development of negative pressure inside it, thus causing a decrease of the boiling point: the evaporated anesthetic in the syringe would force liquid anesthetic to be pumped in boluses in the device (“autopumping”) leading to severe overdose [13]. It should be noted that the system has tidal volume limits beyond which its efficacy is not guaranteed: the tidal volume ( $V_t$ ) should be at least 300 mL and no more than 1000 (which rarely happens), the limit being consistent in some patients in need of protective ventilation with  $V_t$  that may be lower than 300 mL. Also, the adjunct 100 mL of dead space may prove difficult to manage in children. Ambient pollution concerns are common to each device and are discussed below.

Finally, the ACD is incompatible with desflurane because of its high solubility and vapor pressure. This leads to condensation of the product immediately after vaporization.

### 7.2.2 The MIRUS™ System

The impossibility of desflurane to be administered via the ACD was a major drawback because of its more favorable and fast kinetics [5, 16] and lower impact on cardiovascular stability than sevoflurane, all features that matter when critically ill patients are involved [17, 18].

The MIRUS™ system (Pall Medical, Dreieich, Germany) is a new device for inhaled anesthesia delivery in the ICU and the only capable of working also with desflurane. It comprises a reflector filter like the ACD but comes with an integrated

vaporizer, with no need for an external syringe and a dedicated monitor for pressure, flow, and dose measurement. The latter obviates issues the ACD had because it measures the exact end-expiratory concentration of the anesthetic of choice instead of mistaking it for peak concentrations of the anesthetic in the respiratory circle. The desired end-tidal concentration can be set automatically to a target value, and the speed of wash-in rate of the agent can be controlled (thus modifying the velocity at which dosage adjustments are made).

The MIRUS<sup>TM</sup> control unit displays an anesthetic-specific vaporizer unit. The machine is connected via a 100 mL multilumen cable to an interface that is placed between the Y-piece and the tracheal tube: the reflector and a filter, which also act as an HME, are housed here. The filter also contains conduits for gas injection and for gas pressure measurement and flow and concentration assessment. The vapor is administered by phasic injection when the start of inspiration is expected, extrapolating from measurement made from the preceding breathing cycles into the high-flow connecting piece between the control unit and the interface where the vapor quickly equilibrates.

As shown, this novel system shows limitations similar to the ACD while addressing some of the issues with ACD itself. Healthcare workers' exposure and pollution, however, should be always considered.

### **7.2.3 The Zeus<sup>®</sup> Closed-Circuit Anesthesia Workstation**

Finally, the Zeus<sup>®</sup> Infinity<sup>®</sup> Empowered (Dräger, Lübeck, Germany) is the latest model of the closed-loop Zeus<sup>®</sup> anesthesia workstation that allows ICU-like ventilation modes and a direct injection device for volatile agents (DIVA<sup>TM</sup>) to administer inhaled anesthetics following a target-controlled anesthesia strategy. The closed-circuit breathing system uses high-flow wash-in periods to deliver fresh gases and inhaled anesthetics and periodically washes out nitrogen, thus allowing superior stability of VA delivery and the possibility of setting an end-tidal anesthetic target. These features make the Zeus<sup>®</sup> viable for sedation and ventilation purposes in the ICU. The earliest Zeus<sup>®</sup> apparatus was studied in artificial models and displayed fast inhalational agent kinetics, high control over VA administration, and less consumption than traditional workstations [19], so this improved version (Zeus<sup>®</sup> Infinity<sup>®</sup> Empowered) is theoretically suitable for ICU use and could be useful for patient sedation and ventilation in a single integrated device.

### **7.2.4 Safety of Halogenated Anesthetic Use on Healthcare Workers and the Environment**

From the beginning of volatile anesthetic use, problems arose regarding scavenging of exhaled remains of anesthetic compounds as they were known to be toxic for people exposed for long periods, such as healthcare workers, and polluting for the environment [20–22]. The tolerated exposure limits are not uniform around the

world. The American National Institute of Occupational Safety and Health (NIOSH) recommends that, in case of isoflurane, exposure should not exceed 2 ppm of any halogenated agent. In most European countries, the exposure level for occupational safety of isoflurane amounts to 10 ppm over a work shift.

These past issues can be solved observing some standards. Room air turnover is recommended to be at least ten times per hour in order to minimize occupational exposure: the average ICU has poor air conditioning compared to the operating room, so this should be kept in mind [13]. Anesthesia gas scavenging (AGS) systems used in operating room ventilators can be applied to ICUs provided with a central scavenging line; otherwise a residual gas filter can be used.

Three different residual gas filters are widely commercialized: a totally active carbon filter (Aldasorber, Shirley Aldred & Co Ltd), an active carbon filter with part coconut shell fibers (Novasorb, NovaMed GmbH, Düsseldorf, Germany), and a combined active carbon/zeolite filter (Contrafluran, Zeosys, Berlin). The filters have different capacities and thus are differently durable [7].

The Cardiff Aldasorber Medical Filter (Aldasorber, Shirley Aldred & Co Ltd) is a classic active carbon filter. The filter weighs 1200 g when unused and weight increment must be assessed periodically during use. The absorption capacity is reached with a final weight of 1400 g. The filter has a maximum duration of use of 48 h [7].

The Novasorb filter (NovaMed GmbH) has a maximum duration of use of 72 h, longer than the Aldasorber. A German report on efficiency testing of the Novasorb filter reported the assumed MAC of 80 mg/m<sup>3</sup> was not exceeded using sevoflurane. Thus, leaving the residual gas filter to stand for 72 h in a direct filtering environment, the diffusion sampler was not able to observe that the limit had been passed even after 360 min, while mean MAC was 41 mg/m<sup>3</sup> [7].

A new generation of residual gas filters, consisting of a mixture of active carbon and zeolites, were developed to facilitate environmentally friendly handling (Contrafluran, Zeosys). Zeolites are microporous, hydrophilic mineral absorbent agents and are used to separate and store rising residual gas quantities of volatile anesthetic from the exhaled gas. After recovery and filtering, the anesthetic is then resupplied to the system as a pure substance. Moreover, zeolites have an organized pore system with defined pore diameter, so they work like a steric-selective filter: molecules with a diameter greater than the pore diameter are not absorbed. The storage capacity and purity of the mixture absorbed are thus higher, especially combined with the active carbon. These new filters can be used up to 5 days depending on the quantity and type of anesthetic. Also these systems visually display the efficiency of the filter by a colored LED display, a further safety expedient.

Implementation of scavenging and filters has greatly reduced exposure and recent studies recommend their use [23]. Environmental pollution is often measured and within the recommended limit when using the ACD properly [22, 24]. New and simpler scavenging systems are developed and studied even in ongoing trials [25], and reports of their efficacy are already available [26], thus making this once problematic aspect into an easily manageable task.

### 7.3 Volatile Anesthetics for Sedation of the Critically Ill

An ideal sedative agent would have rapid onset of action, provide adequate sedation, allow rapid recovery after interruption, be easy to administer, avoid drug accumulation, display few adverse effects, interact negligibly with other drugs, and be cost-effective. The use of such an agent in the environment of an ICU poses additional issues as patients' conditions are complicated by one or more organ impairments that variously influence the kinetics and action of the chosen sedative. Sedation in the ICU is used to improve tolerance of mechanical ventilation and other invasive practices, relieve patient anxiety, and in some cases support treatment by reducing stress and oxygen consumption of the target organ. Volatile agents may have some advantages over intravenous sedation. A summary of positive and negative features of these agents is presented in Table 7.1.

#### 7.3.1 Evolution of Volatile Anesthetic Use for Sedation in the Intensive Care Unit

Volatile anesthetics were studied in comparison with intravenous sedatives in many randomized controlled trials, often distinguishing between short-term sedation and long-term administration (more than 48 h on average). Early evidence by Kong et al. on 60 patients of a mixed medical and surgical ICU reported more satisfactory

**Table 7.1** Comparison of advantages and disadvantages of sedation with volatile agents (VA) (Modified from Jerath et al. [27])

Issue	Advantages of VA	Disadvantages of VA
Pharmacokinetics and pharmacodynamics	Rapid onset of adequate sedation Rapid pulmonary clearance with minimal metabolism Favorable and fast weaning No accumulation/tachyphylaxis Bronchodilator effects Anticonvulsant effects	Systemic vasodilation Nausea/vomiting, delirium, shivering Cerebral vasodilation (ICP rise) Malignant hyperthermia
Technical features	Flexible titration Direct monitoring of an effect-site dose surrogate (end-tidal concentration) Devices adaptable to every ICU ventilator	Need for specialized equipment Minimum tidal volumes required Scavenging (debatable) Pollution and toxicity for healthcare workers (debatable)
Other effects	Therapeutic preconditioning and postconditioning effect on the heart, lung, kidney, and liver	Neurocognitive impairment of the developing and elder brain Cancer recurrence (debatable)

ICU Intensive care unit, ICP intracranial pressure

level of sedation for isoflurane against midazolam and a shorter time to extubation while also finding a progressive reduction in plasma catecholamines in patients sedated with isoflurane [27]. Spencer et al. investigated longer administration, from 24 up until 96 h, in the same setting on 60 subjects and found again superior quality of sedation and faster extubation with isoflurane compared to midazolam, with no difference in hemodynamic stability [28]. The first trial to assess the efficacy of isoflurane against propofol was a crossover study by Millane et al., in which 24 critically ill patients were sedated for at least 48 h [29]. No difference was found in terms of achievement of the desired sedation level, but the authors advocate technological advancement, recognizing this as a major issue in VA use in ICU. The earliest study to compare desflurane to propofol for short-term sedation was authored by Meiser et al., who also related the level of sedation to bispectral index (BIS) monitoring (target level was under 60). In this population of 60 patients of a postsurgical ICU, time to emergence from sedation, simple order performance, and extubation was shorter with desflurane. Patients sedated with desflurane also recovered cognitive functions faster (orientation, memory) [30].

Prior to year 2003, delivery of VAs in the ICU was the main technical problem in the face of an effective, or at least non-inferior, sedation strategy. Innovation came with the previously described ACD, which managed to facilitate VA dose titration, monitoring, consumption, and scavenging and advanced also the implementation of more precise study protocols.

Sackey et al. experimented sedation with isoflurane via ACD in 40 ICU patients who were allocated to isoflurane or midazolam sedation for 32–52 h, with consideration for any technical issue. Time within target sedation was comparable, but extubation delay was significantly shorter with isoflurane. No difficulties arose with the ACD and no worrisome adverse event was reported. Similar findings with positive opinions regarding the practical use of the ACD were pointed out in subsequent trials including a cohort using isoflurane [31] and two, a crossover and a randomized trial, comparing ACD-delivered sevoflurane with propofol for short-term sedation [24, 32]. Finally, long-term sedation with sevoflurane compared to propofol and to midazolam was the object of a medium-sized RCT performed in a mixed ICU by Mesnil et al. [33]. Again proportion of time within desired interval of sedation score (Ramsay score) was comparable between groups, but wake-up time, extubation delay, and morphine consumption during the 24 h following extubation were significantly lower in the sevoflurane group than in groups propofol and midazolam. Some hallucination episodes were reported with propofol and midazolam, none with sevoflurane, and no hepatic or renal adverse events were reported.

The most recent short-term sedation randomized trials comparing ACD-delivered sevoflurane with propofol were all performed in cardiac ICUs on larger cohorts (100–157 patients) [34–36]. They all found a shorter time to extubation with inhaled anesthesia but no difference in hospital and ICU length of stay while also reporting no difference in adverse effects manifestation (nausea, vomiting, shivering) albeit a need for more vasopressors given sevoflurane's vasoplegic effect. Cardiac endpoints were also evaluated, namely, troponin reduction after cardiac surgery with Hellström et al. reporting no difference at a prespecified time point but a trend toward less



troponin increase with sevoflurane and Steurer et al. showing a lower level of the cardiac biomarker at day 1 postoperative. Interestingly, a study randomizing patients to receive sevoflurane or propofol as the main anesthetic agent during coronary artery bypass surgery and as postoperative sedation found no significant improvements in the extent and time course of myocardial damage biomarkers (troponin among them) compared to propofol [37]. Conversely, another trial with an identical design, apart from a third group in which anesthesia was conducted with sevoflurane and ICU sedation with propofol, found a reduction of N-terminal pro-BNP and troponin levels after off-pump coronary artery bypass grafting [38].

Isoflurane was earlier investigated in the cardiac surgical ICU only in a medium (40 patients) cohort trial that showed a good safety profile and shorter weaning from mechanical ventilation than those sedated with intravenous drugs including fentanyl and midazolam. Recently, only Jerath et al. used it in a cohort of the large randomized trial described above [35] with no significant adverse effects reported and showing the same benefits over propofol as sevoflurane did. Isoflurane may be far from being abandoned as a sedative strategy in ICU, particularly after a significant piece of evidence by Bellgardt et al. In this very recent work, the authors did a retrospective review of data of 200 critically ill surgical patients from a single ICU to investigate mortality at the longest follow-up available. Patients admitted from 2005 to 2010 were all ventilated and sedated continuously for more than 96 h with isoflurane-ACD or propofol or midazolam and followed up until 1 year after discharge: in-hospital mortality was 40% versus 63% ( $P = 0.005$ ) and 1-year mortality 50% versus 70% ( $P = 0.013$ ), respectively [39]. Despite the limitations of this study, these original results warrant more investigation and foster speculation on nonsedative effects of inhaled anesthetics.

One of these hypotheses is the widely debated preconditioning and postconditioning effect [40]: there is a wide body of literature describing the power of VAs in preventing and even repairing organ damage caused by ischemia-reperfusion, probably via antioxidant properties. Evidence on the cellular mechanism [41] and model animals [42] of pre-/postconditioning effect populates recent literature, but also on the clinical side (chiefly, but not only, in the cardiac surgical setting), VAs are attributed to neuroprotective [43], cardioprotective [44–47], and lung [48], renal [49], and liver [50] protective power. It remains unclear which administration strategy shows the highest efficacy, i.e., whether short-term, high-dose exposure (like during general anesthesia) before the ischemic insult or longer-term, low-dose protocols (as in Bellgardt's study and in general during ICU sedation) after reperfusion damage have different protective properties on which organ [51].

### **7.3.2 Limitations to the Use of Volatile Anesthetics in the Critically Ill**

As above noted, patients from the ICU pose special issues when administered VAs due to their critical status, a condition that may be worsened by the adverse effects of these drugs to lethal effects.

A well-known effect common to all VAs is dose-dependent systemic vasodilation. This leads to concerns in the acutely ill and poses relative contraindications to the use of inhaled anesthetics as it worsens organ perfusion, promotes cerebral vasodilation raising intracranial pressure (ICP), and may aggravate systemic shock. In fact, evidence reports slight increases in ICP, albeit not clinically significant, while advising caution in patients with high baseline ICP values and reduced MAP [52, 53]. This is logically critical in the neurosurgical/neurologic ICU for ischemic and hemorrhagic stroke patients, where adequate sedation may take an excessive toll on ICP [54] and historically discouraged this strategy [55]. As evidence in the field comes from small observational cohorts, larger and higher-quality studies are warranted to definitely establish a recommendation, even more so in the face of the superior control over dosage guaranteed by new delivery systems, such as MIRUS™. Intraoperative reports of goal-directed sedation with BIS monitoring state that less vasopressors are needed to control hypotension when sevoflurane administration is guided by BIS (leading to a striking 50% reduction in volatile dose) [56], and need for vasopressors is anyway not increased during ICU sedation with volatiles, as evidence states [37, 57, 58]. Thus, a superior control from devices and careful monitoring of sedation with BIS or end-tidal concentration [59] could guarantee safe administration of inhalational anesthetics even in fragile patients.

Other side effects of VAs include shivering, nausea and vomiting, and a purported toxicity for the liver and kidney. Meta-analyses of all published RCTs found no differences in the incidence of any of these during ICU sedation, although the lack of such adverse events did not lead to early discharge from the ICU compared to propofol or midazolam sedation [57, 60]. Kidney toxicity was feared mostly because of the accumulation of inorganic fluoride seen with volatile anesthetics exposure. In fact, this is a very well-investigated outcome in early until recent studies, but none of them ever reported an increase of fluoride over 50 mmol/L, the toxic level recommended in most European countries, and likewise no incidence on renal function for either long- or short-term administration [17, 18, 61, 62].

Serious adverse events such as long-term cognitive impairment, malignant hyperthermia, and even cancer recurrence with the use of inhalational anesthesia and sedation are extremely rare, but the catastrophic or ominous occurrence of such complications warrants the physician to be always vigilant, even more so now that long-term administration in the ICU is a feasible practice.

Cognition is a critical issue for some patients after general anesthesia and thus sedation. The elderly, diseased, and developing brain has been shown to be vulnerable to sedatives, so it is imperative to study the long-term impact of volatile agent use in this and every case. Preclinical knowledge states that neurodegeneration in the developing brain is a feature of inhaled anesthetics and appears to be persistent [63–66], although a commentary suggested ischemia-reperfusion could be the real cause [67]. In contrast, Takagaki et al. found that isoflurane compared to propofol suppressed cortical spreading depolarization in rats, an electroencephalographic feature thought to be a major mechanism of delayed brain injury in stroke and brain trauma and capable of predicting patient outcome [68]. Clinical knowledge reports mixed evidence. Short-term follow-ups yielded no significant differences in patients'

cognitive functions measured with screening questions and tests for signs of post-traumatic stress disorder (PTSD) [69, 70]; only one early study reported incidence of a reversible neurologic dysfunctional condition in children [71], and in contrast, a psychomotor dysfunction defined as symptoms including systemic or localized tremor, chorea, and hallucinations was uncommon in adult patients receiving shorter isoflurane infusions [72]. A long follow-up study evaluated the same endpoints with several cognitive scales and found less hallucinations with isoflurane compared with midazolam for sedation in the critically ill [69].

A very recent line of research suggested VA could favor cancer recurrence [73]. The idea stemmed from early preclinical evidence [74] and was studied and reviewed increasingly afterward as in a RCT which assessed superior immunosuppression (including antitumoral natural killer cells) caused by sevoflurane compared to propofol [75], a prospective testing of pro-tumoral protein expression in patients exposed to VA compared to total intravenous anesthesia [76] and others summarized in recent meta-analyses of preclinical [77] and clinical observational studies [78], with conflicting results. Higher-quality research and longer follow-up are needed to explore this dreadful hanging sword.

A rare but devastating complication as malignant hyperthermia (MH) is strongly connected to inhaled anesthetics use in predisposed patients, a characteristic that is often unpredictable [79]. Strong suspect of the occurrence of MH should be rapidly met with immediate change of the ventilator circuit, dantrolene infusion, artificial cooling, and confirmation by genetic and muscle biopsy testing. However, this condition remains rare (1/50,000–100,000), and moreover, efforts for more refined and swift clinical protocols are emerging in higher-risk populations [80].

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## **7.4 Special Applications of Volatile Anesthetics in the Intensive Care Unit**

### **7.4.1 Pediatric Patients**

Anesthesia with VA in children has a long history, while the same cannot be told of volatile sedation within the pediatric intensive care unit (PICU). One more time the advent of the ACD and the superior control over inhaled agents infusion it provided spurred clinical experimentation in the field, with Sackey et al. reporting three cases of sedation with isoflurane in the PICU: two children with abdominal complications switched to isoflurane sedation for several days after prolonged sedation for mechanical ventilation and one who received isoflurane as an extreme treatment refractory status epilepticus. Both sedation and treatment were adequate, and ACD proved feasible and handy to use in these patients [12].

A larger case series by Eifinger et al. of children aged 12 months on average reports similar satisfaction again switching to isoflurane for over 7 days, after 9 days of common sedation, and collected more outcomes: ketamine and clonidine infusion rates were significantly reduced after the switch as well as the use and overall infusion rate of midazolam,  $\gamma$ -hydroxybutyrate, fentanyl, and morphine [81]. The

authors still advise caution with the risk of neurodegenerative toxic effects of isoflurane on the developing brain, as explored before [72].

The field needs further attention and matching caution. It remains clear that volatile anesthetics have superior advantages in sedation qualities and are paramount for therapy in specific conditions (discussed further) [82]. Furthermore, older sedatives like midazolam recently raised concerns in neonates admitted to the ICU [83] as ICU stay, neurologic complication like leukomalacia and intracranial hemorrhage, and inadequate analgesia were higher compared to placebo/morphine.

### 7.4.2 Volatile Agents as Therapy: Status Epilepticus

VAs provide effective sedation and may have organ protective power via antioxidant properties that protect against ischemia-reperfusion injury. Still, not every ICU is a postoperative ICU, and other nonsedative properties of these drugs could be used for treatment of critical conditions where other strategies may have failed. In fact, volatile anesthetics (especially sevoflurane and isoflurane) are potent anti-inflammatory drugs, antiepileptics, and bronchodilators.

The antiepileptic properties of volatile anesthetics may find a place in treating refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE), two severe medical conditions with limited treatment options and high morbidity and mortality. The RSE and SRSE are defined by continued seizures after adequate anticonvulsive therapy with at least two or three antiepileptic drugs, respectively. Aggressive pharmacological and non-pharmacological therapeutic options were tried, including ketamine, intravenous immunoglobulin G (IVIG), steroids, hypothermia, ketogenic diet, and even transcranial magnetic stimulation, electroconvulsive therapy, and vagal nerve stimulation. Isoflurane and desflurane also were used to suppress RSE and SRSE: as these drugs undergo significantly less metabolism than other sedatives, they induce less organ toxicity, and thus they are considered first choices. The interesting action here would be potentiation of GABAA receptor conductivity and inhibition of NMDA receptors [84].

Mirsattari and colleagues analyzed the use of inhaled anesthetics in severe SRSE patients in a large retrospective review. Isoflurane and desflurane proved to be able to induce burst suppression in all patients. Unfortunately, seizures reoccurred once the inhaled anesthetics were stopped. Volatile agents showed adverse effects too, including hypotension requiring IV vasopressor support, infection, paralytic ileus, deep vein thrombosis, and cognitive dysfunction with prolonged use, albeit questionable [85].

### 7.4.3 Volatile Agents as Therapy: Status Asthmaticus

Status asthmaticus (SA) is a severe, refractory form of asthma that can lead to progressive respiratory failure. Despite the gravity of this medical condition, many patients take advantage of standard therapy (beta2-adrenergic agonists and

corticosteroids). Others show an asthma which proves refractory to traditional treatment, too, and may take advantage of adjunctive therapy like inhaled anesthetics.

Volatile agents have a rapid onset and have the power to relax the bronchial muscle lining, dilating constricted airways and thus reversing bronchoconstriction. Gas exchange and peak inspiratory pressure are improved, while the incidence of ventilator-induced lung injury (VILI) is reduced.

Volatile agents may offer support to lung protective ventilation for acute respiratory distress syndrome (ARDS), a breathing strategy which is a widely validated treatment for these cases. Sedation of such patients is often lengthy, which is why inhaled anesthetics may be a valid alternative to intravenous drugs [86].

Inhaled agents can reduce lung injury, according to preclinical models of ARDS. The use of isoflurane in a rat model of ARDS showed lower levels of inflammatory mediators in the bronchoalveolar lavage (BAL) [87], while in a porcine model of acute respiratory distress syndrome, sevoflurane enhanced the response to lung inflammation reducing the neutrophil count and improving oxygenation [86].

However, human data regarding this specific topic is still lacking [88]. Only a recent randomized controlled trial by Jabaudon et al. on ARDS patients proves that sevoflurane for ICU sedation, compared to midazolam, limits epithelial injury and inflammation and leads to a better oxygenation [89]. This field of research may be promising but is now purely experimental.

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## Conclusions

Volatile agents are among the possible sedative strategies in the ICUs. Their use might be lifesaving in severe asthma and in refractory status epilepticus. Evidence-based medicine is suggesting that they reduce time on mechanical ventilation when compared to other agents. Costs are now competitive, new devices are user-friendly, and safety and pollution issues have been solved. It is reasonable to foresee an increased use of these agents in the ICUs.

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# Regional Anaesthesia Techniques for Pain Control in Critically Ill Patients

## 8

Francesco Forfori and Etrusca Brogi

### 8.1 Introduction

In the intensive care unit (ICU), several mechanisms can explain the pathophysiologic origins of pain. Intense nociceptive signals arising from damaged tissues (i.e. invasive procedures, surgeries, trauma, inflammation) are detected by nociceptors. Then, the nociceptive afferent pathways are activated, and the pain signals are transmitted towards the central nervous system and the efferent neural branches. Furthermore, patients can be admitted to the ICU with a pre-existing chronic pain condition (i.e. neoplasm, terminally ill patients, fibromyalgia, spondylosis), or they can develop chronic pain syndromes during their ICU stay, presumably from ineffectively treated or recurrent pain experience [1].

Pain relief represents primarily a right for our patients. Additionally, pain control is fundamental for reducing nociception-induced responses, which may negatively influence organ functioning and contribute to morbidity. Nociception triggers a variety of adaptive physiological and behavioural reactions through neuroendocrine mechanisms, sympathetic activation and the subsequent general stress response [2]. Pain-induced responses include anxiety, tachycardia, tachypnoea, diaphoresis and increased catabolism leading to an increased myocardial oxygen consumption/demand and to an activation of the pituitary-adrenal axis. Furthermore, at the site of the injury, several inflammatory mediators are released (e.g. prostaglandins, cytokines, bradykinin), and the immune system is also activated. As a consequence, pain may result in immune system dysfunction, hypercoagulable states and altered metabolic control. Noteworthy, in patients with chest trauma, thoracotomy and abdominal injuries, inadequate pain control is associated with ineffective coughing and chest breathing and, consequently, with the development of atelectasis, consolidation and respiratory failure [3].

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In light of this evidence, it is fundamental to achieve an adequate pain control. A multimodal approach to pain management has to be chosen in order to reduce physiologic stress and to accomplish an optimum patient comfort. A multidisciplinary approach should include pharmacological-specific options as well as non-pharmacological interventions. The integration of physiotherapy for improved joint movement and prevention of muscle wasting, a meticulous nursing care to reduce patient discomfort (i.e. positioning, management of secretions) and the prevention of disrupted sleep quality to maintain circadian rhythm are extremely effective measures to implement in the treatment programme. An effective pain management aims not only to reduce pain intensity but also to optimize drug doses and decrease the opioid side effects (i.e. nausea, vomiting, urinary retention, respiratory depression and sedation). Pain is often difficult to assess and to quantify (e.g. sedation, endotracheal tube, cognitive impairment), and alternative assessment tools are available to guide pain management (i.e. changes in heart rate and blood pressure, sedation (Ramsay score), behavioural abnormalities) [4].

Regional anaesthesia has become precious for the treatment of pain during and after a wide range of surgical and painful invasive procedures at the bedside. Even more, its benefits have been observed also for the management of trauma-related issues. The alleviation of pain associated with breathing in patients with thoracic trauma and rib fractures has demonstrated to provide an enhancement in respiratory function (improving cough, deeper breathing and relaxation of bronchial smooth muscle), to shorten the mechanical respiratory support and to accelerate weaning from mechanical ventilation [5]. Thoracic epidural analgesia, paravertebral blocks and continuous intercostal nerve blocks are effective for this purpose. In trauma clinical setting, regional anaesthesia could also represent useful aids for evacuations and transportation of the patients. Moreover, regional anaesthesia has shown to provide interesting anti-inflammatory and antithrombotic effects and to improve gastrointestinal and hepatic microcirculation [6]. Another positive advantage of using regional analgesia technique includes the reduction of opioid use and side effects and, consequently, the prevention of narcotics-related delirium and cognitive dysfunction and a reliable cognitive status assessment in patients with traumatic brain injury. Regional analgesia techniques should always be considered in ICU patients especially when the systemic use of narcotics is contraindicated or when the nociceptive stimuli are well confined to specific anatomic regions (i.e. thoracotomy, rib fractures, upper or lower extremity orthopaedic procedures). The placements of epidural catheters (thoracic or lumbar) or peripheral nerve blocks (upper or lower extremities nerve block) are effective manoeuvres to manage these sources of pain. Nevertheless, regional anaesthesia presents special challenges in ICU (i.e. coagulopathies, infections, increasing the risk for local anaesthetic systemic toxicity, sedation).

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## 8.2 Regional Anaesthesia Techniques

Regional anaesthesia consists of several single shots or continuous techniques. Local anaesthetics are administered in close proximity to peripheral nerves and plexus or directly into spinal fluid with a needle (single-shot techniques) or through catheters (continuous techniques). Central neuraxial anaesthesia and the placement

of peripheral catheters should be considered to provide longer and durable pain control. Otherwise, depending on the location of a planned intervention, a single-shot technique can be utilized for several invasive procedures: wound closure, fracture repositioning, burn treatment, wound debridement and procedures involving extremities. Furthermore, skin infiltration with local anaesthetics is the most commonly utilized method to provide analgesia during the placement of lumbar drains, chest tube and invasive lines (i.e. arterial line, central venous catheter). Topical local anaesthesia can be performed with spray nebulizer, with direct cotton swabs or inhaling aerosolized local anaesthetic, and it is essential in order to achieve optimal local neural blockade for several invasive procedures at the bedside (i.e. awake fibre-optic intubation, gastroscopy, bronchoscopy). An overview of indications, contraindications and complications of regional anaesthesia technique is provided in Table 8.1.

**Table 8.1** Regional anaesthesia techniques in critically ill patients

	Indications	Contraindications	Complications
Epidural anaesthesia	Chest trauma, thoracic and abdominal surgery, major orthopaedic surgery, acute pancreatitis, cardiac surgery	Coagulopathy and anticoagulated patients, sepsis, local infections at the puncture site, severe hypovolemia, acute haemodynamic instability, raised intracranial pressure	Bradycardia, hypotension, epidural haematoma or abscess, accidental intrathecal puncture/administration
Paravertebral block	Breast surgery, thoracic surgery, abdominal surgery, rib fractures, treatment of chronic pain	Coagulopathy and anticoagulated patients, sepsis, local infections at the puncture site, untreated contralateral pneumothorax	Infections, haematoma, nerve injury, total spinal anaesthesia, paravertebral muscle and quadriceps muscle weakness
Intercostal block	Thoracic or upper abdominal surgery, rib fractures, breast surgery	Infection at the injection site, coagulopathy or anticoagulation, severe pulmonary dysfunction, sepsis, uncooperative patients, untreated contralateral pneumothorax	Risk of pneumothorax, laceration of intercostal vessels
Intrapleural analgesia	Rib fractures, pain treatment for chest and upper abdomen, herpes zoster, complex regional pain syndromes and pancreatitis	Infection, emphysema, bullous lung disease, recent pulmonary empyema, pleural adhesion or pleurodesis, haemothorax, coagulopathy, contralateral phrenic nerve paralysis	Pneumothorax, local anaesthetic toxicity, airway depression, respiratory inadequacy, phrenic nerve paralysis

(continued)

**Table 8.1** (continued)

	Indications	Contraindications	Complications
TAP block	Postoperative analgesia for laparotomy, appendectomy, laparoscopic surgery, abdominoplasty, gynaecological procedures and caesarean delivery	Infection at the procedure site, allergy to local anaesthetics, neuropathy	Intraperitoneal injection, bowel and hepatic injury
Iliohypogastric and ilioinguinal nerve blocks	Somatic procedure for lower abdominal wall/inguinal region, analgesia after surgical procedures using a Pfannenstiel incision	Infection at the procedure site, allergy to local anaesthetics, neuropathy	Transient femoral anaesthesia, perforation of the small and large bowels, pelvic haematoma
Interscalene block	Shoulder, arm and elbow surgery	Infection at planned injection site, coagulopathy, contralateral pneumothorax, contralateral vocal cord and phrenic palsy	Epidural, intrathecal or carotid artery injection of LA, recurrent laryngeal and phrenic nerve blocks
Supraclavicular block	Arm, elbow, forearm and hand surgery	Infection at site of injection, severe coagulopathy, contralateral pneumothorax	Pneumothorax or phrenic nerve block and phrenic nerve palsy
Infraclavicular block	Elbow, forearm, hand surgery	Infection at injection site, severe coagulopathy, contralateral pneumothorax	Pneumothorax, interference with subclavian line, bleeding
Axillary block	Forearm and hand surgery	Local infection at the puncture site	Vascular puncture, infection, nerve injury
Femoral block	Anterior thigh, femur and knee surgery	Local infection at the puncture site, neuropathy	Haematoma, infection, vascular puncture, nerve injury
Sciatic block	Foot and ankle surgery, analgesia after knee surgery	Infection at site of injection, neuropathy	Nerve injury, infection, bleeding, haematoma

### 8.2.1 Regional Anaesthesia for Endotracheal Intubation

Knowledge of regional anaesthesia techniques for the airway is required for awake fibre-optic intubation in patients with cervical spine fractures or with suspected difficult intubation. Despite the presence of new devices, awake fibre-optic intubation represents an essential skill that every anaesthetist has to master. Several international guidelines recommend awake fibre-optic intubation in patients with predicted difficult airway [7–9]. First of all, it is essential to decide a proper approach: nasal or oral routes. Each of these routes has a specific innervation pathway that has to be



specifically blocked to provide adequate anaesthesia. During the endotracheal intubation, specific regions will be encountered by the bronchoscope and the endotracheal tube; consequently, it is important to soothe specific reflexes for simplifying the manoeuvre and improving patient comfort. Careful preparation is essential before awake fibre-optic intubation procedure. Bland sedation is critical to reduce anxiety preferable using short-acting reversible agents. Furthermore, antisialagogues should be administered in order to reduce oral secretions. Then, the neural blockade of that region is achieved using topical anaesthesia with spray nebulizer or with direct cotton swabs. Otherwise, topical anaesthesia of the oropharynx can be obtained inhaling aerosolized local anaesthetic. Adequate time distribution is needed to achieve optimal conditions. Then, the flexible bronchoscope is introduced (through nasal or oral routes) and advanced. When the epiglottis and vocal cords are visualized, local anaesthesia can be administered using the insufflating port of the flexible bronchoscope. More challenging, the block of the glossopharyngeal and superior laryngeal nerves can be used for awake fibre-optic intubations.

### 8.2.2 Central Neuraxial Blocks

Central neuraxial blocks (CNBs) include epidural, spinal, combined spinal-epidural (CSE) and caudal epidural injections. Epidural anaesthesia (EA) can be used to provide both anaesthesia and analgesia. Continuous epidural analgesia represents the most common utilized regional anaesthesia technique in ICU. In order to place correctly an epidural catheter, it is fundamental to understand the anatomy of the epidural space and the relationship between spinal cord segment, spinal nerve and cutaneous dermatome. Notably, the anatomy and the size of the vertebrae modify along the length of the spine. The epidural space lies between the dura mater and the walls of the vertebral canal and extends from the foramen magnum to the sacrococcygeal ligament. The midline approach and the palpation of anatomic landmarks (spinous process) represent the standard technique for central neuraxial blockade, and the epidural space is accessed through the vertebral interlaminar space, into the interspinous ligament; otherwise, a paramedian approach can be chosen. Then, the operators rely on their tactile sensation, during needle advancement, to identify proper epidural access. However, spinous processes are not always easily identifiable especially in obese patients, in pregnancy, in case of spinal deformity or previous spinal surgery. The use of ultrasound (US) for epidural catheterization improves success rate and safety. With the application of ultrasound, it is possible to identify and understand the anatomy of the epidural space and, consequently, to assess the correct puncture site and the depth of needle insertion (Fig. 8.1). Ultrasound guidance has shown to reduce the number of puncture attempts, to improve the success rate of epidural catheterization and to decrease the need to change dermatome levels.

The beneficial effects of the use of epidural analgesia are widely recognizable. Epidural anaesthesia (TEA) has been described to improve pulmonary dynamic function and to facilitate weaning from the ventilator after lung surgery and thoracic trauma [5]. In fact, in this kind of patients, thoracotomy produces a significant



**Fig. 8.1** Spinous processes of the lumbar vertebrae in longitudinal plane

reduction of postoperative pulmonary function. Even more, the pain has the potential to worsen lung dynamics [3]. Providing adequate analgesia, TEA can improve pulmonary functionality and respiratory parameters and can reduce the recurrence of chronic pain especially in patients with chest trauma and post thoracotomy [5, 10, 11]. Furthermore, TEA is thought to provide a positive cardioprotective effect [12]. TEA can produce a selective segmental blockade of the cardiac sympathetic innervations (T1–T5) and may enhance coronary perfusion, improve myocardial oxygen balance and reduce perioperative arrhythmias and myocardial ischemia [13, 14]. However, the role of TEA in cardiac surgery is still debated especially for the possible complications of this anaesthetic technique and the use of systemic anticoagulation needed during cardiopulmonary bypass. Noteworthy, epidural anaesthesia (thoracic and lumbar) seems to have other important beneficial effects, including anti-inflammatory effects, bowel motility enhancement and the reduction of the incidence of deep venous thrombosis and thromboembolism [15]. Major surgery is associated with hypercoagulable and pro-inflammatory state that persists in postoperative periods. The mechanisms responsible for these reactions are considerably complex (i.e. sympathetic nerve activity, sepsis, immune response, stress, impaired microcirculation and intrahepatic inflammatory reaction). EA has shown to present protective effects against these detrimental consequences especially on hepatic, pancreatic, bowel and coagulation functionality [16]. The sympathetic block of TEA and its anti-inflammatory effects seemed to be the major mechanisms of its protective properties [6, 17, 18]. Several Cochrane and meta-analysis have confirmed the abovementioned benefits of EA in comparison to opioid-based pain control (i.e. better pain relief, reduce duration of tracheal intubation, facilitate weaning, reduce cardiac complications, prevent gastric and renal impairment) [19, 20]. However, these reviews failed to demonstrate a positive impact of epidural analgesia on mortality [21–23].

EA is indicated in several types of surgeries (as shown in Table 8.1). A combined spinal-epidural approach can be useful when sacral anaesthesia is needed at the beginning of the surgery, and an epidural analgesia is desired at the end (i.e. urological, perineal, gynaecologic surgery). An alternative approach to epidural space is

through the sacral hiatus. The caudal approach is used mainly in paediatric practice; however, it can be used for anaesthesia and analgesic purpose also in adult patients. The caudal epidural block is suitable when anaesthesia of lumbar and sacral dermatomes is required (i.e. perineal and perianal surgery, rectum surgery, cystoscopy and urethral surgery, haemorrhoidectomy). This block can be also useful for the management of chronic pain (i.e. diabetic polyneuropathy, post-herpetic neuralgia, complex regional pain syndrome, orchialgia). Continuous spinal anaesthesia (CSA) is not widely used for postoperative analgesia, mainly to avoid complications from the subarachnoid injection. Particular attention has to be made on the maintenance of sterile injection, and the patients' neurological status should be evaluated at regular intervals. Not to be underestimated, the placement of epidural or spinal catheter presents specific contraindications (as described in Table 8.1). Particular caution should be used in case of patients taking anticoagulants. A more comprehensive description of the regional anaesthesia management in patients receiving antithrombotic drugs is available in several guidelines [24, 25]. A summary of indicated time intervals between administrations of antithrombotic drugs and performance of neuraxial blockade or catheter removal following the 2013 recommendations of "The association of Anaesthetists of Great Britain & Ireland, The Obstetric Anaesthetists' Association, Regional" [26] is provided in Table 8.2.

**Table 8.2** Time intervals between administrations of antithrombotic drugs and performance of neuraxial blockade or catheter withdrawal following the 2013 recommendations of "The association of Anaesthetists of Great Britain & Ireland, The Obstetric Anaesthetists' Association, Regional Anaesthesia UK" [26]

	After neuraxial blockade	Catheter in place	After catheter removal
UFH sc	4 h	Caution	1 h
LMWH sc (prophylactic dosage)	12 h	Caution	4 h
LMWH sc (therapeutic dosage)	24 h	Caution	4 h
Fondaparinux (prophylactic dosage)	36–42 h <sup>a</sup>	Not recommended	6–12 h
Fondaparinux (therapeutic dosage)	Not indicated <sup>a</sup>	Not recommended	12 h
Warfarin	INR $\leq 1.4$	Not recommended	After catheter removal
Dabigatran	48 h <sup>b</sup>	Not recommended	6 h
Aspirin	No contraindications	No additional precautions	No additional precautions
Clopidogrel	7 days	Not recommended	6 h
Prasugrel	7 days	Not recommended	6 h
Ticagrelor	5 days	Not recommended	6 h
Abciximab	48 h	Not recommended	6 h
Tirofiban	8 h	Not recommended	6 h

UFH unfractionated heparin, sc subcutaneous, LMWH low molecular weight heparin, INR international normalized ratio, CrCl creatinine clearance

<sup>a</sup>Consider anti-Xa levels

<sup>b</sup>CrCl > 80 ml.min<sup>-1</sup>

### 8.2.3 Paravertebral Block, Intercostal Nerve Block and Intrapleural Analgesia

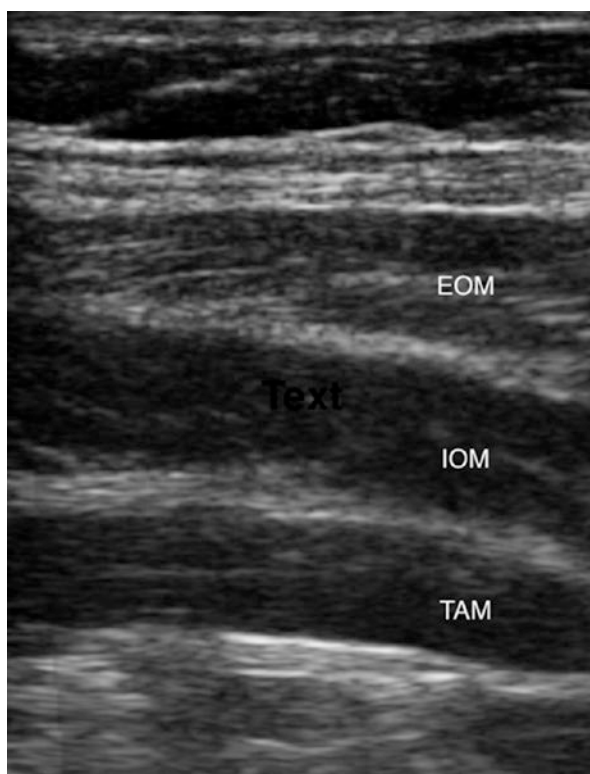
The thoracic paravertebral space (PVS) is a wedge-shaped area that lies on either side of the vertebral column. This area is bounded by the parietal pleura (anterolaterally), by the vertebral body (medially) and by the superior costotransverse ligament (posteriorly). The PVS contains the dorsal and ventral rami of the spinal roots as well as sympathetic fibres. Consequently, paravertebral block (PVB) can provide unilateral motor, sensory and sympathetic block. The spinal nerve exits from the intervertebral foramina and then divides into dorsal and ventral rami. The dorsal ramus provides innervation to the skin and muscle of the paravertebral region. The ventral ramus continues laterally as the intercostal nerve. Noteworthy, the thoracic paravertebral space is continuous with the intercostal space laterally, epidural space medially and contralateral paravertebral space (through the prevertebral fascia). Consequently, the injection of local anaesthetic into the paravertebral space can result in lateral extension of the drugs along with the intercostal nerves or a medial extension into the epidural space through the intervertebral foramina. The lumbar PVS is confined within the iliopsoas (anterolaterally), vertebral body (medially) and the superior costotransverse process (posteriorly). Paravertebral block (PVB) provides unilateral trunk anaesthesia. The dermatome distribution of anaesthesia or analgesia depends on the level blocked and the volume of local anaesthetic injected. Operators have to identify the anatomic landmarks: spinous processes, transverse process and lower tips of scapulae (corresponds to T7). Constant attention to the depth of needle insertion is essential to avoid pneumothorax or neuraxial space entrance. Ultrasound guidance can be used to help identify the PVS and needle placement and to monitor the spread of the local anaesthetics. Ultrasound represents a valid help for avoiding pneumothorax. PVB provides adequate analgesia in patients with unilateral rib fractures and after thoracotomy, with less cardiovascular and respiratory effects in comparison to central neuraxial blocks [27]. A catheter can also be inserted for continuous infusion of local anaesthetic.

Intercostal nerve block represents (like PVB) an alternative to spinal or epidural anaesthesia for chest and abdominal pain control. As described above, the ventral ramus of the thoracic spinal nerve continues laterally as the intercostal nerve. This nerve travels along the subcostal margin of the rib, inferiorly to the intercostal artery and vein. Operators have to identify the following anatomic landmarks: twelfth rib, the seventh rib, spinous process, angle of the rib (6–8 cm lateral to the spinous process) and the intercostal space. The extent of the resulting dermatomal distribution of local anaesthetic depends on the level of blockade. In order to achieve proper pain control, operators have to block one additional level above and one beneath the estimated dermatome levels. After having identified the puncture site, the needle is advanced below the inferior margin of the rib pointing caudally (in order to prevent intercostal vessel injuries). Intercostal block produces sensory anaesthesia of the thoracic wall in the respective dermatomes for 12 h without a sympathectomy block. Unilateral intercostal block is useful in reducing drug requirement during thoracotomy, for relieving pain of fractured ribs and for management of postoperative pain. Furthermore, continuous and multilevel intercostal nerve blockade seemed to significantly improve pulmonary function and pain control in patients with rib fractures [28].

Intrapleural block consists of infusing local anaesthetics between the parietal and visceral pleura. This block provides unilateral block of multiple thoracic dermatomes. It is described to be effective in unilateral pain control from the chest and upper abdomen. Local anaesthetic can be administered as single shot or through an indwelling catheter. Intrapleural block depends on local anaesthetic spread through the intrapleural space and requires significant volumes of local anaesthetic. It is particularly influenced by local anaesthetic concentrations and patients' position. Problems related with this block are pneumothorax and loss of local anaesthetics via chest drains. For the aforementioned reasons, this block is not commonly used in ICU.

#### 8.2.4 TAP Block and Iliohypogastric and Ilioinguinal Nerve

The transversus abdominis plane (TAP) block can be used to provide ipsilateral analgesia to the anterior abdominal wall. The abdominal wall consists of three muscle layers (i.e. external oblique, internal oblique, transversus abdominis muscles) and the corresponding fascial sheaths (Fig. 8.2). Local anaesthetics are injected between the transversus abdominis and internal oblique muscle planes. The spread of LA is variable and is influenced by several factors; however, this technique



**Fig. 8.2** Transverse ultrasound anatomy of the abdominal wall

theoretically can block the anterior rami of the lower six thoracic nerves and the first lumbar nerve (from T7 to L1). The TAP block could be performed following a loss-of-resistance technique or using ultrasound. The blind approach consists of the injection of local anaesthetic into the triangle of Petit (i.e. the area narrowed within the iliac crest, the latissimus dorsi and the external abdominal oblique muscle) [29]. The injection site is identified by tactile sensation during needle advancement. A first “pop” reveals the access between the external oblique muscle and internal oblique muscles. Then, a second pop is felt when the needle penetrates the fascia of the internal oblique muscle. Otherwise, using US, the transducer can be placed between the iliac crest and costal margin at the mid-axillary line. Then, the three muscle layers should be visualized, and the needle is inserted in-plane in a medial to lateral orientation. A different approach, defined as the subcostal approach, can be performed to achieve analgesia for the upper abdomen.

For this approach, the ultrasound probe is placed parallel to the subcostal margin near the xiphoid process. Furthermore, a combination of the posterior and oblique subcostal techniques (with four-point, single-shot technique) has been found to provide good bilateral analgesic coverage after abdominal surgery. The spread of local anaesthetic is influenced by the different approaches (posterior, subcostal) used, as well as by the volume of local anaesthetic injected; it seemed to have an important impact on the effectiveness of pain control [30, 31].

Several meta-analyses have been published on the possible role of TAP block in providing analgesia after different kinds of surgeries [32, 33]. In these trials, the TAP block showed to reduce 24h pain score, morphine consumption and the incidence of PONV; however, when TAP block was compared with intrathecal morphine (ITM), ITM demonstrated to provide greater analgesic efficacy [34]. Nevertheless, TAP block can be used as alternative pain management technique when neuraxial techniques or opioids are contraindicated. TAP blocks can be performed either at the beginning (i.e. preemptive analgesia) or at the end of surgery. However, the relatively short duration of analgesia (24–48 h postoperatively) and the wide variability in LA spread represent the major real concerns with TAP block.

The iliohypogastric and ilioinguinal nerves are branches of the first lumbar nerve (L1). The two nerves emerge from the psoas muscle at its upper lateral border and then cross obliquely the quadratus lumborum. At the level of the iliac crest, the nerves enter the transversus abdominis muscle and run between it and the internal oblique muscle. The iliohypogastric nerve divides into two branches that supply the skin of the superior pubic area and the gluteal skin and the anterior cutaneous and lateral cutaneous branches. The ilioinguinal nerve enters the internal oblique muscle and crosses the inguinal canal and then emerges from the superficial inguinal ring to supply the skin on the superomedial aspect of the thigh and pubic area. The nerves have both sensory and motor functions. Ilioinguinal and iliohypogastric nerve blocks can be performed following the landmark technique or using ultrasound. Local anaesthetic administration is performed 2 cm medial and superior to the anterior superior iliac spine. Once the skin puncture site is individualized, the needle is inserted perpendicular to the skin. As described for TAP block, a 2-pop sensation (loss of resistance) technique is used to identify the site of injection. The first loss of

resistance is felt as the needle enters through the external oblique muscle and the internal oblique muscle. A further loss of resistance is appreciated once the needle passes through the internal oblique and the transversus abdominis muscles. The local anaesthetic is administered after the first and the second loss of resistance. Alternatively, the use of ultrasound allows directly visualizing these muscular layers and accurate injection of local anaesthetic both between the transversus abdominis and internal oblique muscles and between the internal oblique and external oblique muscles.

Ilioinguinal and iliohypogastric nerve blocks have been shown to significantly reduce pain associated with herniorrhaphy [35]; however, these blocks do not provide visceral anaesthesia; consequently the surgeon has to infiltrate the sac (containing peritoneum) with LA to complete anaesthesia for the procedure. An indwelling bilateral catheter can be used for continuous postoperative analgesia for procedures using a Pfannenstiel incision.

### **8.2.5 Stellate Ganglion Blockade**

A stellate ganglion block consists in injecting local anaesthetics in the sympathetic nerve tissue of the neck. The stellate ganglion is a sympathetic ganglion situated on the either side of the neck, at the level of the sixth and seventh cervical vertebrae, and is formed by the fusion of the inferior cervical ganglion with the first thoracic ganglion. A stellate ganglion block can be either diagnostic (to find the cause of a patient's pain) or therapeutic. The stellate ganglion blockade is effective in the management of pain (in the head, neck, chest or arm) caused by nerve injuries or by herpes zoster, in treating sympathetic maintained pain and complex regional pain syndrome. During a stellate ganglion block, the patient is usually sedated, and local anaesthetic can be injected using US guidance.

### **8.2.6 Peripheral Nerve Block for the Upper Extremities**

The brachial plexus can be blocked by different approaches: interscalene, supraclavicular, infraclavicular and axillary nerve blocks. Each block has specific advantages and risks. The interscalene approach is ideal for arm and shoulder surgery. This block results in anaesthesia of dermatomes C5–C7 and can also result in anaesthesia of the cervical plexus (C2–C4), supplying the skin over the acromion. However, this approach is occasionally ineffective in the C8–T1 dermatome (ulnar side of the hand); consequently, it is not recommended generally for hand surgery. For classic blind technique, the main landmarks for this block are the clavicular head of the sternocleidomastoid muscle, the clavicle and the external jugular vein. Otherwise, an US transducer can be placed in the transverse plane at the level of the cricoid over the interscalene groove. The brachial plexus is visualized lateral to the carotid artery. Potential complications are represented by epidural, intrathecal or carotid artery injection of LA, recurrent laryngeal nerve or phrenic nerve block.



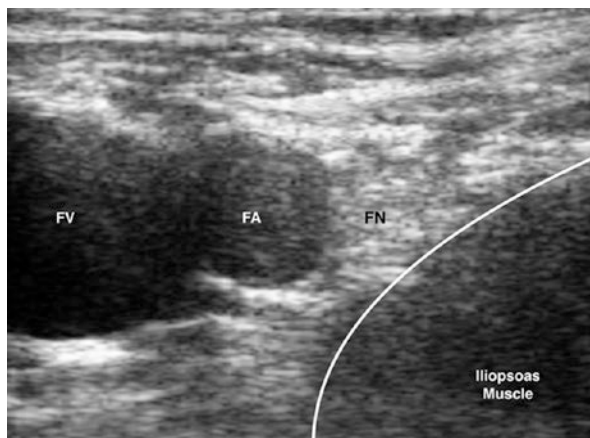
The supraclavicular approach to the brachial plexus results in anaesthesia of dermatomes C5 through T1 and provides anaesthesia or analgesia of the entire upper extremity. For blind technique, the main landmarks for this block are the lateral insertion of the sternocleidomastoid muscle onto the clavicle and the clavicle itself. Otherwise, an US transducer can be positioned in the transverse plane immediately superior to the midpoint of the clavicle. The brachial plexus appears as a bundle of hypoechoic structures lateral to the artery. The proximity of the brachial plexus to the pleura and the subclavian artery has been the major concern for practitioners. However, ultrasound guidance and the consequent ability to identify vital structures have increased the safety of this approach. An indwelling catheter can be inserted to provide continuous postoperative analgesia.

The infraclavicular block approaches the nerve from below the clavicle. This block provides anaesthesia of the hand, wrist, forearm, elbow and distal arm but not on the skin of the axilla and of the proximal medial arm (intercostobrachial nerve). The main landmarks for this block are the medial clavicular head and coracoid process. The US approach is based on obtaining a short axis view of the subclavian artery; the nerve is just lateral to the vessel. Finally, the axillary block represents the safest approaches to brachial plexus. It provides anaesthesia for the three nerves of the hand (radial, median, ulnar), but this block does not provide analgesia for the shoulder. The patient is placed in supine position with the arm abducted at 90°. The main landmark is the pulsation of the axillary artery. Nerves can be visualized in a short axis view using ultrasound.

The aforementioned blocks can be used not only for pain control after surgery and invasive bedside procedures but also for pain management in patients with fractures and joint dislocation. These blocks provide pain relief and muscle relaxation. Continuous brachial plexus blocks have shown to promote prolonged analgesia and superior patient satisfaction after surgery and trauma [36].

## **8.2.7 Peripheral Nerve Block for the Lower Extremities**

The femoral nerve block can provide adequate analgesia for the anterior thigh and in the saphenous nerve distribution without the haemodynamic changes associated with neuraxial blocks. For the blind technique, the landmarks are the inguinal crease and the femoral artery pulse. For US femoral nerve blocks, the transducer has to be placed at the level of the inguinal crease. The femoral nerve appears as a hyperechoic structure (triangular or oval in shape) just lateral to the femoral artery, medial to the iliopsoas muscle and deep to the fascia iliaca (Fig. 8.3). The needle is inserted in-plane in a lateral-to-medial orientation and advanced towards the femoral nerve. Careful attention has to be made in the visualization of the spread of local anaesthetic around the nerve, between the two layers of fascia iliaca; needle repositions may often be necessary. Additionally, the sciatic nerve block can provide good analgesia to the posterior thigh and the distal lower extremity. Different approaches are described for this nerve block: anterior, transgluteal and subgluteal approaches. Even more, the sciatic nerve can be blocked at the level of



**Fig. 8.3** Cross-sectional anatomy of the femoral nerve

the popliteal fossa (called “the popliteal block”). A combination of femoral and sciatic block can be effective for the pain management after lower limb surgeries. Finally, the lumbar plexus block (LPB) is an advanced nerve block technique. The main challenges for achieving an effective LPB are related to the depth and the size of the plexus. This block requires the placement of the needle in the deep muscles and is burdened with high risk of systemic toxicity. Furthermore, the proximity of the lumbar nerve roots to the epidural space also carries a risk of epidural spread of the local anaesthetic.

Low extremity trauma or injuries are common conditions in ICU patients. Peripheral nerve blocks for the lower extremities can be used as anaesthetic technique or as perioperative pain management after orthopaedic surgery. Major benefits are good pain control, early mobilization and no need of urinary catheterization. Furthermore, a continuous infusion of LA through an indwelling catheter is helpful in the management of acute pain following femoral fractures or surgical stabilization. Even more, a good pain control seems able to prevent phantom limb pain or other chronic syndromes in trauma patients [37].

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### 8.3 Special Considerations in ICU Patients

Regional anaesthesia techniques encounter particular challenges in ICU patients. Several coexisting factors can increase the difficulty to properly individualize the needle insertion site for nerve block. Patients’ position, the occurrence of anasarca and the presence of several catheters and monitoring devices are common confounding factors that can impede to perform successfully a nerve block in ICU. Noteworthy, nurses must be comfortable with the management of the catheters used for continuous infusion in order not to confuse the administration routes. Frequent inspections have to be done to prevent infectious complications.

Altered state of coagulation is a common condition in ICU. Trauma, surgery, massive transfusion, sepsis and many other potentially life-threatening conditions have the potential to activate both haemostasis and the inflammatory immune system, leading to an increased risk for the development of thrombocytopenia and post-operative bleeding. The haemodynamic consequences and the bleeding complications related to specific regional anaesthesia techniques are not to be underestimated. In this scenario, the benefits-risk ratio of performing the different regional anaesthesia techniques has to be estimated case by case. Furthermore, several guidelines (as aforementioned explained) have been published on the regional anaesthesia management in patients receiving antithrombotic drugs [24, 26].

Several factors may contribute to the occurrence of LA toxicity in critically ill patients: individual comorbidity, concomitant medications, site of injection, specific type of local anaesthetic (e.g. bupivacaine, ropivacaine), total local anaesthetic dose or a combination of the aforementioned factors. Patients with liver disease present a reduced LA metabolism, whereas in severe renal impairment, there is a reduction in LA clearance. Patients with severe cardiac failure are particularly vulnerable to LA-induced arrhythmias. Even more, pregnant patients are at an increased risk of toxicity due to accelerated absorption of LA at the injection site. Hypoalbuminemia is frequent in critically ill patients and actually leads to a reduction in drug binding and an increase of the free/active drug concentration. Electrolyte imbalance and alterations of acid-base homeostasis have a significant impact on increasing the likely of the toxicity of local anaesthetic occurrence. Furthermore, the site of injection of LA plays a major role in the incidence of systemic toxicity, because some sites have a higher risk of direct intravascular injection (e.g. interscalene block) and others are at increased risk of rapid absorption due to a highly vascularized area.

Compartment syndromes can be a dramatic consequence of trauma to the extremities. Traditionally, it was thought that postoperative pain control with regional anaesthesia technique may mask the early symptom and delay diagnosis of this syndrome. Recent trials seemed to confute this belief [38].

Performing regional anaesthesia in heavily sedated patients is still controversial. Some authors believe that heavy sedation increases patient acceptance and decreases injuries consequent of patient movement. On the contrary, other authors reckon that, in case of heavy sedation, patients are unable to report early warning signs of local anaesthetic toxicity and neurological injury. However, we have to take into account that an appropriate sedation can decrease the risk of seizures (increasing the threshold level of neurological toxicity). Prevention of LA toxicity requires not to reach specific LA plasma concentration levels; consequently, the most effective method to prevent systemic toxicity (both neurological and cardiovascular toxicity) is to inject slowly, using incremental dose of LA and to perform “the test dose” (with epinephrine) in order to identify unintentional intravascular LA injection. Even more, the use of US allows the visualization of the different structures surrounding the nerve and consequently to avoid intravascular or intraneural injection. US allows to observe the spread of local anaesthetic and the needle placement and to make appropriate adjustments. This feature reduces the total volume of LA used. However, the Second ASRA Practice Advisory on Neurologic Complications Associated with

Regional Anesthesia and Pain Medicine did not recommend to perform routinely regional anaesthesia techniques in heavy sedation because, up to now, there is no evidence that US guidance reduces the risk of neuraxial injuries in heavily sedated patients [39].

Lastly, the geriatric patients warrant special attention. This population presents an increase in pain threshold level but a decrease in pain tolerance. Pharmacokinetics is also altered in elderly patients. Indeed, there is an alteration in volume distribution, clearance and elimination of the drugs; consequently, the LA dose requirement is reduced and therapeutic window narrowed. The use of narcotics and sedatives can lead to delirium and cognitive dysfunction. It is vital to titrate accurately drug dose and to choose a multimodal approach to pain control especially in this kind of population [4].

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## 8.4 Ultrasound Imaging Techniques for Regional Blocks

Bedside point-of-care US guidance for nerve localization during nerve blockade has brought important changes in clinical practice. US provides real-time imaging and allows detecting nerve roots and defining surrounding structures. Before attempting a nerve block, operators have to acquire a basic knowledge of the sonographic appearance of different tissues, of the functionality of the ultrasound machine (knobology), the rudiments of manipulation of the US probe and needle visualization/orientation within the US beam. The appearance of nerves is variable. Typically, peripheral nerves appear as a “honeycomb” structure. The hypoechoic structures are the fascicles of the nerves, while the hyperechoic images are the connective tissue between neural structures. Generally, nerves appear as round, oval or triangular shape when visualized in short axis view, whereas in long axis view, they appear as longitudinal structures. Other structures that can be visualized are vein (anechoic, collapsible under pressure with US transducer), artery (anechoic, pulsating, not collapsible), fascia (hyperechoic layers), muscles (hypoechoic with striate structure) and bones (hyperechoic border with hypoechoic acoustic shadow) [40]. Depending on the type of block performed, gain, penetration, depth, frequencies and image resolution must be optimized. Adequate identification of neuronal and adjacent anatomical structures should be achieved prior to needle insertion. Remarkably, it is important to visualize vital structures (i.e. vessels and pleura) in order to avoid unintentional puncture. Then, the needle can be inserted in-plane (the needle passes through the long axis of the US beam) or out of plane (the needle passes through the short axis of the beam) and advanced towards the nerve. Trajectory changes and needle repositions may often be necessary. Once the needle is in place, the local anaesthetic is administered under direct sonographic visualization until the nerve is surrounded by LA. Consequently, US guidance allows the administration of adequate volumes of local anaesthetic and prevention of intravascular drug administration. Technical issues arise from specific blocks. Lumbar plexus is technically challenging to visualize, and the epidural space and the spinal cord are often obscured by the acoustic shadow. However, the advantages of using US are several,

including the ability to recognize both the target and vital structures and redirect the needle to optimize the trajectory. Furthermore, the effective identification of the LA spread around the nerve allows a reduction of the total amount and volume of drugs administered. To conclude, the current evidence shows that the use of US reduces the number of puncture attempts, improves the success rate at the first attempt, reduces the need to multiple puncture attempts, reduces the incidence of complications and improves patient comfort during regional anaesthesia procedures [41, 42].

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## 9.1 Introduction

Neuromuscular blocking agents (NMBAs) are widely used by anesthesiologists and intensivists in many clinical situations. Whereas in the operating room (OR), curarization is maintained for a limited period, in intensive care unit (ICU), it can last for days or weeks. In addition, the physiology of the critically ill patient is different from that of the ordinary surgical patient.

### 9.1.1 Sedation in ICU

Sedation is typically used in those patients who present agitation or anxiety due to pain, discomfort, hemodynamic instability, etc. Different levels of sedation can be achieved, from light (patient can be awakened) to deep (not arousable even with painful stimuli).

### 9.1.2 Neuromuscular Blockade in ICU

Neuromuscular blockade (NMB) in ICU is quite common (up to 13% of patients mechanically ventilated) and must be titrated on each patient according to clinical needs. Monitoring of NMB and an adequate sedation and analgesia are important to avoid adverse effects.

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## 9.2 Neuromuscular Transmission and Blockade

Movement, and also muscle trophism, is triggered by the interaction between motor neurons and muscle fibers. The contact point between these two structures is represented by the neuromuscular junction, where acetylcholine (ACh) is released from the presynaptic terminal to activate postsynaptic muscle-type nicotinic receptors, allowing the entry of  $\text{Na}^+$  and  $\text{Ca}^{++}$ , and consequently the contraction.

There are also some presynaptic receptors, explaining the drug interaction with other medications:

- Nicotinic: stimulate the further release of ACh; their activation explains the train-of-four (TOF) fade with non-depolarizing blockers.
- Muscarinic: tend to be inhibitory receptors, reducing ACh release. Consequently, the administration of atropine will increase the release of ACh.
- $\alpha$ -Receptors: facilitate ACh release. In patients undergoing infusion of catecholamines, this could lead to a partial curarization.

NMBAs interfere with neuromuscular transmission: their use ranges from induction of anesthesia in ORs up to emergency intubation in ICU. They can also be used in critically ill patients, for example, to treat persistent shivering during therapeutic hypothermia or to improve the treatment of patients with ARDS. They are classically divided into depolarizing and non-depolarizing. The latter can be further divided according to their duration of action (long, intermediate, and short acting).

### 9.2.1 Depolarizing Agents

The only depolarizing agent used in clinical practice is succinylcholine: it is composed of two molecules of ACh linked by methyl groups. Although nicotinic receptor activation is similar to that caused by ACh, succinylcholine is not hydrolyzed by acetylcholinesterase of the synaptic cleft, resulting in prolonged depolarization. The block caused by this drug is divided into two phases:

- Phase I blockade (*depolarizing*): provokes a continuous firing from the motor neuron, often resulting in fasciculation. Succinylcholine seems to exert this action also with a prejunctional binding to nicotinic receptors, enhancing the neurotransmitter release.
- Phase II blockade: tends to appear with elevated plasma concentrations of succinylcholine or when it is administered in continuous infusion (even if at low doses, as in patients defective for plasmatic acetylcholinesterase). This block is characterized by a TOF response similar to that for the non-depolarizing agents. The causes seem to be (1) the maintenance of the resting potential following the activity of the  $\text{Na}^+ - \text{K}^+$  ATPase and (2) the presynaptic blockade of ACh transport. Furthermore, desensitization can occur: ACh receptors become insensitive to the channel-opening effects of agonists.

Adult dose for intubation is 1–1.5 mg/Kg, with an onset of 60 s. Muscle relaxation lasts about 6 (2–10) min, with partial recovery already after 3 min.

The use of succinylcholine is not free from risks: various side effects can occur including muscle pain, tachycardia, bradycardia, ventricular arrhythmias, hypertension, hyperkalemia, and, less commonly, increased intracranial pressure or malignant hyperthermia (in patients with mutations of ryanodine receptor). The mean increase in  $K^+$  is 0.5–1 mEq/L, which would be significant in patients with pre-existing hyperkalemia. A special warning in the case of burn patients, following thermal injury, extra-junctional acetylcholine receptor expression increases in proportion to the magnitude of the burn. This results in an exaggerated release of potassium after administration of succinylcholine.

## 9.2.2 Non-depolarizing Agents

Non-depolarizing NMBA's exert their function on the postsynaptic side, antagonizing ACh in a competitive manner, preventing the conformational change in the receptor, or physically obstructing the ion channels so that an end plate potential is not generated. The non-depolarizing blockade is dynamic (binding and dissociation), so if ACh concentration increases, there is more chance of receptor binding compared to the antagonist. At least 92% of receptors must be occupied to obtain a complete block. Like succinylcholine, non-depolarizing NMBA's also exhibit desensitization block. An effect is also detected in prejunctional nicotinic receptors, resulting in failure of mobilization of ACh. Clinically, this is manifest as tetanic fade and TOF fade, in which there is a reduction in twitch height with successive stimuli. Non-depolarizing NMBA's are structurally divided into aminosteroid compounds (pancuronium, rocuronium, vecuronium) and benzylisoquinolines (atracurium, cisatracurium, mivacurium) [1].

### Aminosteroids

These are formed of a steroidal skeleton with at least one quaternary ammonium group. Some deacetylated metabolites seem to exert a neuromuscular blockade.

*Pancuronium* is a long-acting compound with a long onset time (up to 3 min). It is metabolized in the liver in an active compound 3-hydroxypancuronium and then excreted in bile and urine. Although this drug does not release histamine, adverse effects can include tachycardia, hypertension, and increased cardiac output. These effects can partly counteract those of hypnotics administered for induction of anesthesia.

*Vecuronium* has an intermediate duration of action and onset time (2–2.5 min). It is metabolized by the liver to three active metabolites, all of which are excreted in urine. In patients with chronic kidney disease, this could lead to accumulation and prolonged NMB. Minimal adverse cardiovascular side effects have been reported.

*Rocuronium* is similar but less potent than vecuronium. It has a rapid onset (1–1.5 min) and short-to-intermediate duration of action, around 30–40 min. The drug is eliminated by the liver and the kidneys, and few adverse cardiovascular effects are reported. Rocuronium has no direct sympathomimetic effects but in high doses has a mild vagolytic property. Prolonged use, such as in ICU, causes a half-life extension.

### Benzylisoquinolines

These are formed of two quaternary ammonium groups joined by a thin chain of methyl groups.

*Atracurium* is composed of ten stereoisomers: in fact, by selecting only a few of these, other benzylisoquinoline NMBAs are produced. The onset time is 1.5–2 min, while its action lasts for 35–43 min. The main metabolic pathways are represented by:

- Hofmann elimination (autolysis), pH and temperature dependent
- Non-specific esterases (hydrolysis)
- Renal excretion (of inactive metabolites)

No dosage adjustment is required in patients with hepatic or renal dysfunction. Moreover, according to the Hofmann reaction, acidosis and severe hypothermia decrease the rate of drug metabolism requiring dose adjustment, titrating according to patient's response. Atracurium causes histamine release, leading to hypotension; in addition to this, a sympathetic ganglionic blockade is present.

*Cisatracurium* is a single isomer of atracurium, with an onset time of 2–2.5 min and 45–65 min of predicted action. It is three times more potent than atracurium: this allows the administration of smaller doses, with fewer adverse effects. The main metabolic pathway is represented by Hofmann elimination, leading to the production of laudanosine. Less histamine is released, with lower incidence of cardiovascular adverse effects. Critically ill patients with severe sepsis may have a delayed and reduced response to standard dosing regimens.

*Mivacurium* has an onset of action comparable to that of atracurium (2.2–3 min) but is a short-acting compound (16–23 min) because of rapid hydrolysis by plasmatic cholinesterase. The duration of action could increase in those patients with hepatic or renal insufficiency and consequently depressed plasmatic cholinesterase activity. Small doses (0.15 mg/Kg) do not lead to major cardiovascular adverse effects; however, hypotension could occur in the case of larger doses, because of histamine release. Little information is available about the use of mivacurium in ICU [2]. A comparison is shown in Table 9.1.

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## 9.3 Clinical Use in ICU

### 9.3.1 Sedation and NMB

Regarding daily sedation interruption (DSI), a recent systematic review from Burry Lisa found no strong evidence that DSI alters the duration of mechanical ventilation, mortality, length of ICU or hospital stay, adverse event rates, drug consumption, or quality of life for critically ill adults receiving mechanical ventilation compared to sedation strategies that do not include DSI. However, those results are not conclusive given the statistical and clinical heterogeneity identified in the included trials. Further studies need to be conducted [3].

**Table 9.1** Comparison between principal neuromuscular blocking agents

Drug	Dose	Onset/acting	Metabolism	Adverse effects	Warning
Succinylcholine	B: 1–1.5 mg/Kg C.I.: 36–57 mcg/Kg/min	30–60 s/2–10 min	Plasmatic acetylcholinesterase	Muscle pain, tachycardia, bradycardia, ventricular arrhythmias, hypertension, increase in intraocular pressure, hyperkalemia, malignant hyperthermia	CKD, burn patients, penetrating eye injuries, pre-existing hyperkalemia
Pancuronium	B: 0.05–0.1 mg/Kg A.D.: 0.01–0.02 mg/Kg	150–220 s/75 min	Renal excretion biliary excretion liver (3-hydroxypancuronium)	Hypertension, tachycardia and increased cardiac output due to vagal blockade, reduced intraocular pressure	Increased acting: hypokalemia, hypocalcemia, myasthenia gravis, CKD
Vecuronium	B: 0.08–0.1 mg/Kg A.D: 0.02–0.03 mg/Kg C.I.: 0.8–1.2 mcg/Kg/min	120–180 s/30–35 min	Liver (active compound) Renal excretion	Histamine release, skeletal muscle weakness	Possible cross-sensitivity if previous anaphylaxis with NMBAs. Increased acting: CKD, hepatobiliary obstruction
Rocuronium	B: 0.6–1 mg/Kg A.D.: 0.075–0.15 mg/Kg C.I.: 7–12 mcg/Kg/min	60–90 s/30–40 min	Renal excretion Biliary excretion	Hypotension, tachycardia, histamine release	Possible cross-sensitivity if previous anaphylaxis with NMBAs. Increased acting: CKD, hepatobiliary obstruction, MODS
Atracurium	B: 0.3 e 0.6 mg/Kg A.D.: 0.1–0.2 mg/Kg C.I.: 4.5–13 mcg/Kg/min	90–120 s/35–43 min	Hofmann degradation A specific esterases Renal excretion	Hypotension, histamine release, sympathetic ganglionic blockade	Possible cross-sensitivity with cisatracurium. Increased acting: acidosis and severe hypothermia
Cisatracurium	B: 0.15 mg/Kg (propofol) 0.1–0.4 mg/Kg (opioids) A.D: 0.03 mg/Kg C.I.: 1–3 mcg/Kg/min	120–150 s/45–65 min	Hofmann degradation	Hypotension, bradycardia, histamine release (laudanosine)	Possible cross-sensitivity with atracurium. Increased acting: acidosis and severe hypothermia, isoflurane, halothane, ketamine
Mivacurium	B: 0.25 mg/Kg (0.15 mg/Kg + 0.10 mg/Kg after 30 s) A.D.: 0.1 mg/Kg C.I.: 8–10 mcg/Kg/min	130–170 s/16–23 min	Plasmatic cholinesterase	Histamine release, hypotension, tachycardia, rash, bronchospasm	Increased acting: liver dysfunction, halothane

*B* bolus, *C.I.* continuous infusion, *A.D.* additional dose, *NMBAs* neuromuscular blocking agents, *CKD* chronic kidney disease, *MODS* multiple organ dysfunction syndrome

NMBAs do not have sedative, amnestic, or analgesic properties, so an adequate sedation and analgesia is mandatory before starting the administration of NMBAs. Based on the Richmond Agitation-Sedation Score (RASS), the ideal level of sedation is  $-2$  (light sedation). Non-benzodiazepine sedatives should also be preferred [4].

Furthermore, NMBAs do not prevent muscles from contracting after direct stimulation. Their use in ICU could be useful to enhance mechanical ventilation, improve oxygenation and gas exchange, and diminish the risk of ventilator-associated lung injury. Sedation is useful but not sufficient, especially in nonconventional ventilator strategies such as prone positioning, permissive hypercapnia, high frequency oscillatory ventilation, and the use of high levels of PEEP. In addition to this, transpulmonary pressures are reduced, potentially minimizing the risk of overstretch on alveoli. Other therapeutic uses include preventing movement in patients with increased intracranial pressure, resolution of tetanus, and rapid sequence intubation in emergency situations [5].

### 9.3.2 Mechanical Ventilation and ARDS

Partial neuromuscular blockade facilitates lung-protective ventilation during partial ventilatory support while maintaining diaphragm activity in sedated patients with lung injury [6].

A meta-analysis by Alhazzani et al. found that a 48-h continuous infusion of cisatracurium reduced the risk of death at 28 days, ICU discharge, and hospital discharge. In addition, there is a decreased risk of barotrauma, and no effects are detected in the duration of mechanical ventilation or in the risk of ICU-acquired weakness. The study found that in every nine patients affected by ARDS receiving continuous infusion of cisatracurium, one life is saved during the first 90 days of hospital stay. This magnitude of effect is larger than that achieved with low-tidal-volume ventilation. Furthermore, ventilator-free days were increased in the cisatracurium group, as a result of competing risks of death and duration of ventilation, both of which are integrated into this outcome [7].

### 9.3.3 Sepsis

In a study by Steingrub et al., it has been noted that in septic patients who have undergone mechanical ventilation, early prescription of NMBAs during the hospital course is associated with lower mortality in comparison to those that have not received NMBAs as well as those with retarded treatment. Estimated reduction in mortality associated with receipt of neuromuscular blocking agent therapy was 4.3% (95% CI  $-11.5, 1.5\%$ ) [8]. The Surviving Sepsis Campaign recommends the use of NMBAs  $<48$  h in adult patients with ARDS, as does Murray et al. There are no indications concerning curarization in septic patients, excluding those presenting ARDS [9]. It is important to mention that patients with septic shock, presenting acidosis and multiple organ dysfunction syndrome, tend to have a delayed metabolism for NMBAs.

### 9.3.4 General Considerations

Among the various serious adverse reactions to these drugs, secondary infection and ICU-acquired weakness may place a burden on the health-care system by resulting in substantial cost and long-term morbidity. Modern ICU practices favor lower doses of corticosteroids and a very short course of short-acting curare for the management of sepsis or ARDS. Recent trials provided no evidence for increased risk of secondary infections or critical illness neuromyopathy in patients with sepsis or ARDS with the use of corticosteroids or neuromuscular blockers [10].

### 9.3.5 Discontinuation and Reversal

Discontinuation of neuromuscular blockade must be a gentle process, during which analgesia and sedation adequate for patient comfort must be maintained. Partial reversal of the action of non-depolarizing NMBA's could be obtained with administration of an anticholinesterase drug (classically neostigmine 0.025–0.05 mg/Kg depending on TOF ratio or number of twitches). For neostigmine, doses exceeding 0.07 mg/Kg are unlikely to achieve any additional effect, because no further increase of ACh could be achieved. Side effects of ACh can be prevented with the coadministration of atropine (0.015 mg/Kg) or glycopyrronium bromide (7 mcg/Kg) [11].

Rocuronium and vecuronium, with their steroidal core, can be reversed by administration of sugammadex. Sugammadex is a  $\gamma$ -cyclodextrin with negative charged extension that binds quaternary ammonium of the target NMBA, and it is the first drug of a new class of medications called selective relaxant binding agents (SRBA). The complex resulting from the binding of the two drugs is excreted by the kidney, without any metabolic modification. Sugammadex indicates reversal of NMBA's effects in the perioperative setting; its use in the ICU setting is not well defined so far. Regarding safety issues, the major concerns are bradycardia and allergic reaction. Recommended posology varies from 2–4 mg/Kg (with 1–2 post-tetanic count) to 16 mg/Kg in case of emergency rescue (achievement of a 0.9 TOF ratio in around 90 s) [12].

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## 9.4 Intensive Care Unit Settings

Generally, critically ill patients present organ dysfunction, so benzylisoquinolines may be preferable in ICU patients as they are not affected by renal or hepatic disease. However, Hoffman degradation could be affected by pH and temperature alterations.

Another factor to take into account is the amount of drugs given to ICU patients: several interactions with NMBA's can occur; some of these are shown in Table 9.2 [2].



**Table 9.2** Drug interactions with neuromuscular blocking agents

Effect	Drug	Notes
Enhanced effect of NMBAs	Magnesium	Reduces ACh release
	Potassium	Reduces ACh release/ $K^+$ - $Ca^{++}$ flux
	Lithium	Reduces ACh release
	$Ca^{++}$ -blockers	Reduces neurotransmitter release
	Procainamide	Blocks nicotinic receptor
	Quinidine	Blocks nicotinic receptor
	Inhalational anesthetic	Postsynaptic receptor blockade
	Corticosteroids	Pre- and postjunctional effect (hypothesis)
	Cyclosporine	Inhibit NMBAs metabolism
	Cyclophosphamide	Reduces plasmatic cholinesterase
	Aminoglycoside	Reduces ACh release <sup>a</sup>
	Tetracycline	Reduces ACh release <sup>a</sup>
	Clindamycin	Interferes with muscle contraction
Reduced effect of NMBAs	Vancomycin	
	Furosemide	Increase intracellular-extracellular potassium ratio
	Calcium	Increases ACh release
	Phenytoin	Reduces ACh release/increases ACh sensitivity
	Ranitidine	Increases ACh release/anticholinesterase activity
	B-blocker	Especially seen with atenolol and propranolol
	Furosemide	Increase renal excretion

NMBAs neuromuscular blocking agents, ACh acetylcholine

<sup>a</sup>Not reversible with neostigmine

### 9.4.1 Cardiac ICU and ECMO

In the cardiac ICU setting, many different types of patients are treated, from post-cardiac surgery to post-cardiac arrest. Another feature of this type of ICU is the use of advanced support devices such as intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), etc.

Most of the studies regarding adjuvants to mechanical ventilation are focused predominantly on patients with ARDS; however, observational data suggest that similar interventions are used in patients with acute respiratory failure (ARF) even if the formal ARDS criteria are not met. ECMO, inhaled pulmonary vasodilators, and continuous NMBAs are used despite inconclusive evidence of benefit or possible harm. In recent years, an increase in the use of ECMO, and no change in the use of continuous infusion of NMBAs, was observed.

For NMBAs, the absence of adoption could be attributed to the uncertainty surrounding benefit, the absence of instant patient improvement (increase in oxygenation), or concerns about harm. Although the continuous NMBA trial did not demonstrate an increased risk of critical care polyneuropathy, anecdotal experience or concern about this risk might be driving lack of adoption until further confirmatory evidence shows consistent results. Knowledge of ongoing trials may also

suggest equipoise, which may also be a factor in the lack of adoption seen for continuous NMBAs [13].

In the specific cohort of ECMO patients, the majority receive prolonged infusion of NMBAs, up to 35% for >24 h. However, the infusion of NMBAs requires an increased use of sedatives, for which reason the trend is to reduce the use of these adjuvants [14, 15].

The population seeming to benefit most from the infusion of NMBAs is that of post-cardiac arrest patients. In out of hospital cardiac arrest (OCHA), early NMB that is sustained for a 24-h period is associated with an increased probability of survival; furthermore, the use of NMBAs seems to favor lactate clearance [16].

### 9.4.2 Postanesthesia Care Unit (PACU)

An increased risk of critical respiratory events and a significant prolongation of the stay in the postanesthesia care unit (PACU) are associated with residual NMB. As a result, a TOF ratio  $\geq 0.9$  has been suggested as the minimally acceptable level of recovery of neuromuscular function. This ratio has been proposed because even mild residual paralysis (TOF ratio 0.7–0.9) is associated with pharyngeal and esophageal dysfunction, obstruction of the upper airway, impaired hypoxic ventilatory response, and patient discomfort. Although most patients with residual NMB do not present critical respiratory events, some patients can develop pneumonia or atelectasis, sometimes requiring noninvasive mechanical ventilation (NIMV) or even reintubation [17].

### 9.4.3 Neurological/Neurosurgical ICU

Although in theory NMB can prevent movements that increase intracranial pressure (ICP) as shivering, cough, and suctioning, at the moment, the use of NMBAs in this setting is not well supported. In addition to the potential side effects, curarization could hide posttraumatic seizure activity. The only potential advantage of NMBAs seems to be the ventilation management of traumatic brain injury (TBI) patients. In fact the avoidance of asynchrony with the ventilator could decrease the risk of volotrauma and barotrauma and improves ICP control reducing intrathoracic pressure [18]. The use of NMBAs can also result in subluxation of unstable spinal fractures.

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## 9.5 ICU Monitoring and NMB

### 9.5.1 Neuromuscular Monitoring

NMB may be monitored with a supramaximal stimulation (above 25% of maximal stimulus) of a peripheral nerve and measuring the muscular response to this stimulation. Patterns of stimulation include:

*Single twitch:* a stimulus is applied for a period of about 0.2 ms, at regular intervals. The major limitation to this technique is the need to measure a control twitch before administering the neuromuscular blocking agent.

*Train of four:* in this pattern, stimulation is applied with a frequency of 2 Hz, four stimuli in total. The train of stimuli is then repeated every 10 s. With this kind of monitoring, it is possible to compare the first twitch of TOF with the fourth one (TOF ratio). Monitoring of TOF ratio is important, because a ratio of 0.9 should be achieved before tracheal extubation. With non-depolarizing agents, TOF shows a decrease from the first twitch to the fourth (TOF fade). On the other hand, succinylcholine provokes an equal decrease in all the twitches; with phase II block, TOF fade is observed.

*Tetanic stimulation:* consists in a high-frequency (50–200 Hz) stimulation for a limited amount of time. This pattern of stimulation is very sensitive and can elicit minor degrees of neuromuscular block, which is potentially useful in the postoperative recovery room. However, its use is limited by the fact that tetanic stimulation is extremely painful.

*Double burst stimulation:* two short stimuli of 50 Hz are given; partially paralyzed with a non-depolarizing agent, the response to the second burst is reduced. The ratio of the magnitude of the second stimulus to the first is known as the DBS ratio.

*Post-tetanic count:* this stimulation could be useful in deep NMB block, because tetanic stimulation could elicit a response after the stimulation [19] (Table 9.3).

A major finding from a study by Bouju et al. was that the objective of TOF count of 1 or 2 was obtained in only less than 10% of the measurements when patients are monitored only according to clinical assessment, even though the NMBA infusion rates were in accordance with the recommendations [20].

Rudis et al. compared patients paralyzed with an aminosteroid managed with a clinical assessment with those managed with a TOF for an objective of 1/4. A faster recovery of muscle paralysis and return to spontaneous ventilation, with a decrease in the amount of infused NMBAs, was observed in the TOF group [21].

### 9.5.2 Bispectral Index (BIS)

In BIS monitoring an electrode is applied on the patient's forehead, recording electrical activity from the cerebral cortex. The signal is then converted to a quantitative

**Table 9.3** Different neuromuscular stimuli

Type	Frequency	Duration	Interval	Repetition	Application
Single twitch	0,1 Hz	0,2 ms	1–10 s	10–1 s	Anesthesia induction
Tetanus	50 Hz	5 s		>6 min	
TOF	2 Hz	2 s	10 s	10 s	Induction, maintenance, intubation, awakening, ICU
PTC	50 Hz	2 s		>6 min	Deep block
DBS	50 Hz	40 ms	750 ms	>6 min	Residual curarization

index varying from 100 (awake) to 0 (flatline). Values of 70, 60, 40, and 20 correspond, respectively, to deep sedation, general anesthesia, deep hypnotic state, and burst suppression [22].

The typical setting of BIS monitoring is OR, but the use of prolonged sedation and NMBA moves the field of action also into ICU. BIS may be useful to prevent both awareness and oversedation. However, BIS is not always reliable and must be tailored to the single patient. Currently, clinical decisions made on the basis of BIS monitoring in ICU should be limited to preventing over- or under-sedation in the appropriate clinical settings and to providing feedback on induced burst suppression when continuous EEG is not available [23].

In a retrospective observational study, Tasaka et al. observed that one out of ten critically ill patients receiving therapeutic paralysis may be inadequately sedated. In this study, BIS provided high sensitivity for unarousable to light levels of sedation, but data were insufficient to make solid conclusions about the ability of BIS to detect inadequate sedation [24].

Regarding interaction of drugs with BIS monitoring, curarization by rocuronium during light propofol-remifentanyl anesthesia results in a decrease in BIS values, and a subsequent antagonization of NMB by sugammadex during surgical anesthesia does not result in a change in BIS values [25].

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## 9.6 Guidelines

The 2016 update on NMBA management in the critically ill patient contains the following recommendations:

Early administration of continuous NMBA in the course of acute respiratory distress syndrome for patients with a  $\text{PaO}_2/\text{FiO}_2$  ratio less than 150.

Routine administration of NMBA to mechanically ventilated patients with status asthmaticus should be avoided.

A trial of an NMBA in life-threatening situations associated with profound hypoxemia, respiratory acidosis, or hemodynamic compromise is suggested.

NMBA may be used to manage overt shivering in therapeutic hypothermia.

TOF monitoring could be useful for monitoring NMB but only if incorporated in an inclusive assessment of the patient, comprehensive of clinical assessment.

Peripheral nerve stimulation with TOF alone should be avoided as monitoring in patients receiving continuous infusion of NMBA.

Structured physiotherapy is recommended in patients receiving continuous infusion of NMBA.

A blood glucose level of  $<180$  mg/dL should be the target in all patients receiving continuous infusion of NMBA.

For obese patients, consistent weight (e.g., ideal body weight) should be used to calculate NMBA doses.

NMBA should be discontinued at end-of-life or when life support is withdrawn [26].

## **9.7 Adverse Effects**

### **9.7.1 Infections**

Hospital-acquired infection is a major concern for patients, health-care staff, and policy makers. Some interventions, such as NMBA infusion, are related to an increased risk of infection in ICU patients. NMBAs may inhibit movement of the bronchial ciliary apparatus, with consequent accumulation of secretions. In addition to this, there is an increasing risk of aspiration of oropharyngeal bacterial flora due to the dysfunction of the swallowing reflex. NMB is suggested as an independent risk factor for ventilator-associated pneumonia, both in general ICU patients, in those with traumatic brain injury, and in post-cardiac arrest care. However, a recent trial conducted by Papazian et al. did not report an increased risk of ventilator-associated pneumonia with the use of cisatracurium in patients with ARDS [10, 27].

### **9.7.2 Deep Venous Thrombosis (DVT)**

Recalling the triad of Virchow (hemodynamic changes, endothelial injury, hypercoagulability), it is clear that the critically ill patient with infusion of NMBAs is subject to blood stasis. In addition to this, many ICU patients have at least one of the other risk factors for thrombosis. A recent study of Boddi et al. reported that the use of NMBAs is the strongest predictor for the development of ICU-related DVTs. The same trial reported that educational initiatives to promote DVT prophylaxis (both mechanical and pharmacologic) significantly reduced the prevalence of DVTs. Closer neuromuscular monitoring coupled with protocols to guide titration of NMBAs may also contribute to reducing the DVT prevalence [28].

### **9.7.3 Corneal Abrasion**

Abolition of the blink reflex and paralysis of eyelids can result in drying, scarring, ulceration, and subsequent infection of the eye. From 8 to 60% of the patients admitted to ICU present corneal abrasions. A possible strategy to reduce the prevalence of ophthalmic complication could be the use of eye protection prophylaxis (tear replacement, artificial ointments, eye covers, etc.).

### **9.7.4 Anaphylaxis**

Patients may develop anaphylaxis after the first dose of NMBA due to cross-reactivity with other inciting agent exposures. The allergenic component seems to be the ammonium. Seven consecutive large French surveys over an 18-year period suggested that NMBAs are the most frequent perioperative agents (more than sedatives, hypnotics, latex, antibiotics, and colloids) involved in allergic reactions [2].

**Table 9.4** Comparison between cardiovascular side effects of NMBA

Drug	Heart rate	Blood pressure	Cardiac output
Succinylcholine	+	+	+
Pancuronium	+	+	+
Vecuronium	—	=/— (rare)	—
Rocuronium	+ / —	=/—	=/—
Atracurium	—	—	—
Cisatracurium	=/—	=/—	=/—
Mivacurium	+	—	=/—

### 9.7.5 Cardiovascular Effects

Many adverse cardiovascular side effects are reported with the use of NMBA. The two main mechanisms of those effects are vasodilation after histamine release and sympathetic ganglionic blockade.

While succinylcholine and pancuronium have a predominantly positive effect that may help in counteracting side effects of sedation agents, atracurium and mivacurium are prone to cause a decrease in blood pressure values.

A comparison is shown in Table 9.4.

### 9.7.6 Prolonged Paralysis and ICU-Acquired Weakness

Prolonged paralysis following drug discontinuation results from accumulation of drug or active metabolites or an acute myopathy. It is a rare disorder related to prolonged use (days) of paralytic agents, often in the setting of renal or hepatic insufficiency. Affected patients have flaccid areflexic tetraplegia.

A modest association between the use of neuromuscular blocking drugs and neuromuscular dysfunction acquired in critical illness, including ICU-acquired weakness (ICU-AW), critical illness polyneuropathy (CIP), and critical illness myopathy (CIM), has been reported. The risk of critical illness polyneuropathy was greater in patients with severe sepsis or septic shock or more severe illness [29].

Proposed mechanisms for ICU-AW include disturbances in the microcirculation, protein malnutrition, systemic inflammation, and prolonged immobility. To date there are not enough solid studies that demonstrate correlation with NMBA use. Two recent trials did not identify an increased prevalence of ICU-AW in ARDS patients administered with a 48-h cisatracurium infusion. Future investigations should examine the impact of other factors, such as corticosteroids, sedation use, type, and duration of NMBA [2].

### 9.7.7 Critical Illness Neuropathy and Myopathy

CIP and CIM have an important impact on the outcome of patients in the ICU. They typically cause muscle weakness and paralysis and impair rehabilitation in up to

100% of patients staying in the ICU for at least 4 weeks. CIP/CIM itself may prolong the need for ventilatory support as the phrenic nerve and diaphragmatic muscle can be involved. CIP/CIM is associated with increased ICU and hospital stays and elevated mortality rates [30, 31]. The pathophysiology of CIP/CIM is complex and still unclear. It is hypothesized that increased capillary permeability allows NMBAs to cross the membrane and have direct toxic effects on the nerve or cause functional denervation of muscle.

Most authors agree on aggressive treatment of sepsis as the most important measure to reduce the incidence of CIP/CIM. NMBAs, if indicated, should be used at a minimal dose for as short a period as possible [32].

CIM and CIP together fall under the classification of critical illness myopathy and/or neuropathy (CRIMYNE). A recent Italian multicenter study found that a criterion to identify patients with CRIMYNE is a peroneal compound muscle action potential (CMAP) reduction below two standard deviations of normal value [33]. This meta-analysis by Price et al. suggests a modest association between neuromuscular blocking agents and neuromuscular dysfunction acquired in critical illness; limitations include studies with a high risk of bias [34].

It is important to distinguish between prolonged neuromuscular block from drug overdosage or the effect of drug metabolites and CRIMYNE.

### 9.7.8 Overdosage

Overdosage, as well as the long-term use of NMBAs, can result in the accumulation of drugs or metabolites with intrinsic activity. The drug is stored in the basement membrane of the neuromuscular junction, which then acts as a reservoir; in addition to this, drug clearance decreases. Overdose is not only due to errors in the drug preparation but also to the failure of titration in the case of electrolyte imbalance or acid-based disturbances [35].

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## 10.1 Introduction

Intensivists can use different sedative drugs to reduce patient discomfort and pain relief of critically ill patients admitted to ICU. None of these drugs is clearly superior to the others [1]. The key point is providing an individualized sedation target followed by periodically arousal monitoring that permits avoiding deep sedations, which is usually associated with poor outcome. Indeed, oversedation could be responsible for prolonged mechanical ventilation, cognitive dysfunction up to delirium, and several risky hemodynamic effects, such as arterial hypotension and myocardial depression. On the other hand, undersedation may also cause anxiety and enhancement of sympathetic stress response that includes arterial hypertension, tachycardia, increased endogenous catecholamine activity, and oxygen consumption [2]. When properly applied, the use of the clinical scales to assess the depth of sedation (e.g., Richmond Agitation–Sedation Scale, RASS) seems to reduce the total dosing of sedative medications and, as a consequence, the risk of drug-related hemodynamic impairment [3]. However, the right choice of a given sedative agent requires profound knowledge of the different classes of drugs and their side effects, especially in terms of cardiovascular effects. In this issue the hemodynamic effects of the most common sedative drugs used in ICU are examined.

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## 10.2 Propofol

Propofol is one of the most common intravenously sedative agents used in ICU. Propofol produces a dose-dependent decrease in heart rate, cardiac output, arterial blood pressure, and systemic vascular resistance with mild depression of myocardial contractility [4]. Evidences from scientific literature suggest that propofol could impair the arterial baroreceptor reflex response to hypotension or may have a directly vagotonic activity, causing bradycardia [5]. Claeys Ma found a statistically significant decrease in systolic and diastolic arterial pressures 2 min after the induction of anesthesia and during the maintenance infusion in healthy humans. The reduction of arterial pressure associated with the induction and infusion of propofol is mainly a result of a decrease in systemic vascular resistance without compensatory increases in heart rate or cardiac output [6]. Muzi studied the mechanisms of hypotension produced by propofol and revealed that even an increase in venous capacitance could be involved with a direct action of the drug on the smooth muscles of the veins [7]. Filipovic found that in healthy young subjects in patients with pre-existing diastolic dysfunction, the infusion of propofol seemed to lead a decrease of the early diastolic peak velocity of the lateral mitral annulus (Ea—a tissue Doppler-derived parameter of global left ventricular diastolic performance), producing just a mild impairment of left ventricular relaxation and early filling not clinically significant [8, 9]. A serious adverse effect of propofol is the so-called propofol infusion syndrome, PRIS, that includes metabolic acidosis (base deficit > 10 mmol/L), rhabdomyolysis (with myoglobinuria, acute renal failure, and hyperkalemia), hyperlipidemia, and fatty liver [10]. PRIS can lead to severe hemodynamic derangement, characterized by decreased myocardial contractility, acute refractory bradycardia leading to asystole, and ventricular arrhythmias. PRIS is strongly associated with propofol infusions at doses higher than 4 mg/Kg/h with duration longer than 48 h. Cases of toxicity below the dose indicated and time of infusion are reported. The pathophysiology of this syndrome probably involved an impaired hepatic function causing lactate accumulation, acidosis, lipid microembolization, or accumulation of inactive metabolites [11]. The hemodynamic management usually requires inotropic support, even though refractory conditions can occur. In few cases, extracorporeal membrane oxygenation (ECMO) has been demonstrated a useful therapeutic alternative in the management of hemodynamic derangement of PRIS [12, 13].

## 10.3 Benzodiazepines

Benzodiazepines are GABA (gamma-aminobutyric acid) receptor agonists modulating the release of GABA in the central nervous system and causing a decrease in neuronal excitation. Clinical effects vary depending on the dose used, from anxiolysis to sedation, amnesia, anticonvulsant activity, and hypnosis [1].

### 10.3.1 Midazolam

Hemodynamic effects of midazolam have been studied carefully throughout the past years. This sedative causes mild decrease in systolic and diastolic arterial pressure due to a reduction in systemic vascular resistances and myocardial contractility. Furthermore, venodilatation and transient changes in portal venous blood flow could reduce cardiac filling and venous blood return [14]. Evidences suggest that conscious sedation with midazolam produce an enhancement of sympathetic activity at small doses [15]. Midazolam does not impair sympathetic baroreflex response to arterial hypotension, so the almost immediate reaction is an increasing heart rate and contractility with mobilization of “non-stressed” blood volume (e.g., splanchnic) into the central circulation. The drug contributes to preservation of hemodynamics also in patients with altered cardiac function [14, 16].

### 10.3.2 Lorazepam

Lorazepam has been proposed as an economic alternative to midazolam for long-term sedation of ICU patients. It is a benzodiazepine with a longer elimination half-life, but its metabolites are inactive and do not tend to accumulate. Consequently, this drug is preferred in patients with renal failure: Hemodynamics is similarly influenced by both lorazepam and midazolam [17].

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## 10.4 $\alpha$ -2 Agonists

The increasing interest in  $\alpha$ -2 adrenergic receptor agonists (i.e., clonidine and dexmedetomidine) is based on their anxiolytic, sedative, analgesic, and anesthetic-sparing effects and sympathetic tone-modulating properties in the absence of respiratory depression. These drugs are agonists of *presynaptic alpha-2 adrenoceptors*, *postsynaptic alpha-2 adrenoceptors*, and *imidazoline receptors*. Locus coeruleus is the main noradrenergic neuronal group target, and it has also several connections with the reticular formation involved in vasomotor control. Pharmacological studies have also demonstrated that *imidazoline receptors* located in areas of the medulla are responsible for the central regulation of cardiovascular function. Dexmedetomidine is a highly selective, shorter-acting alpha-2 agonist, with an alpha-2 and imidazoline receptor selectivity almost doubled with respect to clonidine, which is a long-acting partial agonist [18]. Clonidine was considered an alpha-2 agonist model for a long time. After rapid intravenous bolus administration, it showed a biphasic response of arterial pressure with an initial transient hypertension followed by more durable decrease in blood pressure. The first phase is related to an alpha-2 adrenoceptor-mediated peripheral vasoconstriction with a reduction in heart rate that may be caused by the baroreceptor reflex. Conversely, the prolonged hypotensive effect is due to a reduced sympathetic tone and an

enhanced vagotonic action mediated by centrally located alpha-2 adrenergic and imidazole receptors [18]. The hemodynamic profile of dexmedetomidine, when incremental doses were intravenously administered in healthy volunteers, has similar characteristics to that described for clonidine [19–21]. Hypertension with a decrease in heart rate at high plasma concentrations of dexmedetomidine was observed. Conversely, low plasma concentrations led to a decrease in blood pressure and heart rate without clinically relevant respiratory depression, despite its sedative effects. Some studies demonstrated that after the starter dose, the reduction of the mean arterial blood pressure ranged from 13 to 27% and that it could last for a prolonged time [19, 20]. A dose-dependent reduction in circulating plasma catecholamines by 60–80% was observed [22]. Ebert studied the variations of major hemodynamic parameters after intravenous infusion of increasing doses of dexmedetomidine in healthy humans. At low-dose infusion of dexmedetomidine, the author found a decrease in mean arterial pressure by 13% with no significant changes of central venous pressure, pulmonary capillary wedge pressure, mean pulmonary artery pressure, and systemic vascular resistances. At high drug dose infusion (until plasma levels exceeded 5.1 ng/ml), a progressive increase in mean arterial pressure (about 12%) and a decrease in heart rate and cardiac output (29% and 35%, respectively) were reported. In addition, at high dexmedetomidine plasma concentrations, a pulmonary hypertension with significant increase of pulmonary vascular resistance was observed. This effect could be a limiting factor in patients with cardiac failure [20]. Snapir showed that dexmedetomidine had no significant effects on systolic myocardial function in healthy subjects. In addition, the author demonstrated that at high rates of intravenous infusion, the myocardial blood flow, measured using PET (positron emission tomography) scanner images, was matched with myocardial work, without clinically significant mismatch between cardiac oxygen demand and supply [23]. Recent studies suggest to avoid administering a loading dose of dexmedetomidine to prevent adverse cardiovascular effects, such as hypotension and bradycardia [19, 26]. Cases of severe bradycardia leading to asystole were documented [24, 25]. The European Medicines Agency reported that bradycardia is normally transient; it does not usually necessitate treatment and responds to atropine or dose reduction where needed. Attention should be paid in patients with pre-existing bradycardia, severe left ventricular dysfunction, and spinal cord injury (impaired peripheral autonomic activity). Moreover, the heart block grade II or III is considered a contraindication to the use of the dexmedetomidine [26].

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## 10.5 Opioids

An appropriate pain relief control contributes to sedative drug spare and permits to avoid autonomic stress response to pain (tachycardia, hypertension, increased myocardial oxygen consumption), which could potentially worsen or precipitate a cardiac ischemic pathology [27].

### 10.5.1 Morphine

Cardiovascular effects of the morphine are well known, and they include venodilation, peripheral arterial vasodilation with reduced peripheral resistance, slight arterial hypotension, and reduction in heart rate alongside inhibition of baroreceptor reflexes. Orthostatic arterial hypotension and fainting may occur. This circulatory response is associated with pain relief and reduction in cardiac filling pressures and can lead to a decrease in myocardial oxygen consumption. In fact, for many years morphine has been considered a cornerstone of the treatment of pulmonary edema and myocardial ischemia [28].

### 10.5.2 Fentanyl

Fentanyl is a synthetic compound approximately 100 times more potent than morphine, highly lipophilic with a much more rapid onset of action. Fentanyl and its metabolites decrease heart rate and can slightly decrease blood pressure. However, it provides a hemodynamic stability with only minimal depressant effect on the myocardium. For this reason, high doses of fentanyl could be used as major anesthetic for patients undergoing cardiovascular surgery or for patients with impaired cardiac function [29].

### 10.5.3 Remifentanyl

Remifentanyl is a short-acting synthetic agent that for its pharmacokinetic profile differs from all other opioids. It has a rapid onset of 1 min and offset of action with an elimination halftime lower than 10 min. It is characterized by an organ-independent metabolism by nonspecific plasma and tissue esterases, resulting suitably also in patients with kidney or hepatic failure. Remifentanyl does not accumulate even after prolonged infusions [30]. Low-dose administration has no adverse effect on the hemodynamic status in ICU mechanically ventilated patients [31]. Differently from fentanyl, evidence in literature suggests avoiding bolus administration or very-high-dose infusions because of a marked incidence of hypotension, bradycardia up to asystole, especially in patients with coronary artery disease, where severe hypotension may lead to myocardial ischemia [32, 33]. For its unique pharmacokinetic properties, remifentanyl suits very well in different clinical settings like fast-track cardiac anesthesia or in minimally invasive cardiac procedures. It is used particularly in patients with poor cardiovascular function, providing hemodynamic stability and possible shorter postoperative hospital length of stay [34]. Several cases of acute withdrawal syndrome and difficulties in pain control after cessation of continuous infusion of remifentanyl were reported. In these cases, it is possible to observe tachycardia, hypertension, sweating, mydriasis, and myoclonus. According to these evidences, progressive decrement dosages of remifentanyl infusion over 24–48 h may be advisable to prevent withdrawal syndrome [35].



## 10.6 Volatile Agents

Increasing interest is reported about the use of volatile anesthetic agents for long-term critical care sedation in ICU [36]. Volatile anesthetic agents are commonly utilized in the operating room to provide general anesthesia. Recently, their role as sedative agents in ICU is becoming more and more attractive because they are simple to titrate, do not produce active metabolites, and seem to promote a better hemodynamic stability with faster extubation times [37]. Cardiovascular effects of halogenated agents permit to maintain hemodynamic stability even in patients with hypertension and ischemic heart disease [38]. In literature, there is evidence of a certain degree of myocardial protection promoted by sevoflurane. This drug may decrease the inflammatory response after cardiopulmonary bypass is observed by measuring the release of cytokines like IL-6 and TNF-alpha [39]. Sevoflurane seems to improve myocardial function in cardiac surgery patients as revealed measuring left ventricular regional wall motion abnormality with transesophageal echocardiography [40]. Jerath showed that inhaled volatile agent reduced extubation times in comparison with propofol in patients undergoing coronary artery bypass surgery. In addition, the author observed a higher prevalence of vasodilatation with arterial hypotension and higher cardiac output necessitating the use of vasoconstrictors. There were no differences in sedation score, opioid consumption, ICU or hospital length of stay, or patient mortality [41]. Increasing evidences are available about the use of volatile agents in post-cardiac arrest patients treated with targeted temperature management in ICU. It seems that volatile sedation compared with intravenous sedation may provide a shorter time on mechanical ventilation and ICU stay with no differences in neurological outcome [42].

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## 10.7 Sedation and Hemodynamics in Special Conditions

### 10.7.1 Cardiac Surgery Patient Admitted to ICU

Current guidelines suggest avoiding benzodiazepine and preferring dexmedetomidine or propofol as a first-line sedative agent, in order to improve clinical outcome of mechanically ventilated patients admitted to ICU [2]. In post-cardiac surgery patients, Hammaren et al. showed that propofol reduced systemic arterial pressure by decreasing systemic vascular resistance and reducing stroke volume. Moreover, propofol seems to reduce right ventricular afterload (pulmonary vascular resistance) without causing shunt or change in preload [43]. Several studies revealed a decreased incidence of postoperative complications after administration of dexmedetomidine [44, 45]. A recent meta-analysis showed that dexmedetomidine may reduce delirium and extubation times, but it may increase risk of bradycardia compared with propofol in patients after cardiac surgery. No differences were found in the incidence of arterial hypotension, atrial fibrillation, and ICU length of stay [46].

### 10.7.2 Neurosurgical Patient

Adequate cerebral perfusion is a pivotal piece in the clinical management of neurosurgical patients. This maintenance of hemodynamic stability is of great importance in patients admitted to neuro-ICU. The brain could lose its autoregulatory mechanisms due to a number of cerebral injuries. In these patients, continuous deep sedation is indicated for the treatment of severe intracranial hypertension and refractory status epilepticus. However, neurologically ill patients necessitate strict monitoring of neurological status to achieve a pattern of sedation that allows adequate comfort, pain relief, and an arousal condition with concomitant prevention of delirium [47]. Attention should be paid when administering opioids (e.g., morphine or fentanyl) to traumatic brain injury patients because there is evidence dealing with their capacity of increasing intracranial pressure and cerebral blood flow, due to their direct effect on cerebral vessels (i.e., vasodilation). In spontaneously breathing patients, it is important to consider that these drugs can lead to respiratory depression, resulting in hypercarbia and increased intracranial pressure [47, 48]. The benzodiazepines have slight or no effect on intracranial pressure. These drugs provide hemodynamic stability and anticonvulsant effects but facilitate delirium and prolonged weaning from mechanical ventilation. Propofol reduces intracranial pressure in severe head injury patients and decreases cerebral blood flow and metabolism. It may cause systemic hypotension and myocardial depression [47]. Dexmedetomidine offers numerous advantages over lorazepam in these patients, as it maintains arousability also at deeper levels of sedation and prevents shivering, hemodynamic instability, and respiratory depression. In addition, it may provide neuroprotective effects by avoiding excitotoxicity due to reducing sympathetic activity and release of catecholamines. Finally, it reduces cerebral blood flow and metabolic rate of oxygen by cerebral vasoconstriction and stimulation of the locus coeruleus, thus providing natural pattern of sleep [47]. Dexmedetomidine shows its effectiveness for sedation in perioperative period in patients with hypertensive cerebral hemorrhage who undergo craniotomy, preventing major changes of arterial blood pressure that can cause secondary bleeding [49, 50].

### 10.7.3 Septic Patients

Hemodynamics is very often impaired in septic patients. It is characterized by hypovolemia, vasodilation with reduced arterial tone, microcirculatory dysfunction, and myocardial decreased contractility [51]. Guidelines suggest as best practice for sedation and analgesia of septic patients the same recommendations valid for all critically ill patients. In particular, it suggested avoiding benzodiazepines, while it recommended using short-life sedative [52].

### 10.7.4 Sedation Practice During Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is used to treat critically ill patients with severe cardiorespiratory failure who do not respond to conventional therapy. An optimal sedation management is still not well defined. Usually a deep sedation and muscle paralysis during ECMO permits to reduce the risk of catheter dislocation, coughing, or chatter. Sedation also might help to minimize oxygen consumption. Some evidence revealed that there is an important increase in dose requirement for morphine, midazolam, and propofol during ECMO, determining a challenging effort to provide an adequate sedation and analgesia in these patients [53]. It seems that patients on veno-venous ECMO receive higher sedative doses compared with patients on venoarterial ECMO. Future research should explore mechanisms behind these alterations and try to identify sedative agents more appropriate for sedation during ECMO [54, 55]. Recently, some evidences suggest that the administration of low-dose ketamine infusion as adjunctive agent in a patient during ECMO could help to spare opioid and sedative medications [56, 57]. Ketamine is an antagonist of N-methyl-D-aspartate (NMDA) receptors with some activity at other receptors like opioid receptors. Ketamine is widely known as the anesthetic agent producing dissociative anesthesia and presents several properties as the lack of respiratory depression with bronchodilation and analgesic activity. The well-tolerated cardiovascular profile is characterized by a sympathomimetic action with an increase in heart rate, mean systemic and pulmonary arterial pressure, cardiac output, and pulmonary resistances. Mild increase in systemic vascular resistances added with some myocardial depressant effects was observed [58]. For these unique properties, ketamine results suitably in different clinical scenarios, but further studies are needed to investigate the feasibility of ketamine for sedation in patients receiving ECMO support.

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## 10.8 How to Assess Hemodynamics?

In critically ill patients, hemodynamic monitoring is crucial to detect abrupt hemodynamic changes and avoid inadequate oxygen delivery to tissues. The degree of invasiveness of different monitoring systems is related to patients' comorbidities, hemodynamic stability, admission diagnosis, and need to achieve specific hemodynamic targets. The arterial pressure monitoring is not sufficient to guarantee an adequate peripheral perfusion and oxygen delivery, so attention should be paid toward additional parameters. Clinical examination is the first-line approach of the bedside hemodynamic evaluation, and it should include a neurological status assessment, the observation of the color and temperature of the skin, and a capillary refill time test at fingernail pressure [59]. Increased lactate levels may be an indicator of impaired tissue oxygenation as well as a central venous saturation obtained with a central venous catheter [60, 61]. Also, a venous-to-arterial carbon dioxide difference ( $P_{v-a}CO_2$ ) has been shown to be as a marker of tissue perfusion

[62]. Dynamic indexes of fluid responsiveness (e.g., pulse pressure variation and stroke volume variation) can help in optimizing fluid balance [63]. A surrogate marker of global myocardial function is the cardiac output, which can be assessed by different techniques (e.g., thermodilution method, pulse contour analysis systems, transthoracic and transesophageal Doppler, and echocardiography). Due to its invasiveness, the pulmonary artery catheter is usually reserved for selected cases to measure pulmonary artery pressure and wedge pressure. One of the major key points is considering more than one variable looking at the trend of changes to promptly identify abrupt hemodynamic changes that could put the patients at risk of low oxygen delivery.

## Conclusions

Intensivists provide pain relief and comfort to critically ill patients by means of different sedative agents. Deep knowledge of these drugs is mandatory in order to optimize the level of sedation of patients with heterogeneous clinical conditions. Continuous neurologic and hemodynamic monitoring should be recommended to keep hemodynamic stability while obtaining individualized targets of sedation. This would permit accurate titration of different sedatives and prevent drug-correlated hemodynamic negative effects.

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## 11.1 Introduction

The interaction with the central nervous system (CNS) is the most known mechanism associated with clinical effects of sedatives. Nevertheless, the interactions between sedatives and other organs and systems are misleading, and clinical effects of sedatives, other than sedation, are often underappreciated [1]. Among these, sedative-induced immunomodulation is certainly one of the most important, mainly because immune response is intrinsically involved in acute and chronic critical illness mechanisms. The connection between sedation and immunological impairment has been widely considered as merely theoretical for a long period and often neglected during routine clinical practice. However, evidences provided over the last 10 years have renewed interest in this area [1]. Nowadays, the immunomodulatory effects of sedation have been demonstrated to influence the clinical course of preexisting inflammatory processes, such as acute respiratory distress syndrome [2], acute kidney disease [3], and delirium [4], as well as cross talk with other processes, including the coagulation cascade [1]. Due to the high prevalence of sedative and analgesic use in critically ill patients, the physician should be aware of the sedative effects on the immune response. The aim of this chapter is to analyze the known effects of sedatives on the innate and adaptive immune system.

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## 11.2 The Innate and Adaptive Immune System

The immune system is a complicated balance of effectors belonging to the innate and adaptive systems. Innate immunity encompasses a broad range of host defenses, producing an initial nonspecific, stereotyped, and unselective response to a stressful event (either microbiological or not). It is entirely unchanged during evolution and among different species and includes barriers, complement, cytokines, phagocytes and other antigen-presenting cells, and cytotoxic cells [1]. Circulating molecules, such as complement and cytokine proteins, promote direct and indirect effects on the immune system. The former stimulates and amplifies the cascade to produce opsonization and lysis of bacteria, chemotaxis of immune effectors, mast cell activation, coagulation, and inflammatory responses by the classic and alternative pathways [1]. The complement and the membrane attack complex damages the cell membrane to facilitate the pathogen osmotic lysis. On the other hand, pro- and anti-inflammatory cytokines coordinate the responses of different immune effectors, through paracrine and autocrine effects [1]. With the aim of presenting non-physiological and non-self molecules, many different immunologic cells express pathogen recognition receptors (PRR, e.g., Toll-like receptors). The recognition of pathogen-associated molecular pattern (PAMP) receptors and damage-associated molecular pattern (DAMP) by PRR activates other effectors of the innate immune system as well as promotes activation of the adaptive immune system. Considering the overlap existing in biological mechanisms stimulated by PAMPs and DAMP, the activation of the innate immune system through PRR is similar during infection or trauma [1]. Phagocytes (mainly macrophages and neutrophils) and other antigen-presenting cells (e.g., dendritic cells) become activated early in this response, migrate (by chemotaxis) to the infected/damaged site, present PAMP/DAMP, and produce an inflammatory milieu promoting and coordinating other effectors of the immune system. The generation of reactive oxygen species (by way of a respiratory burst) is a central killing mechanism of macrophages, neutrophils, and all other cytotoxic cells [1].

The adaptive (or acquired) immune system is phylogenetically more recent, being presented only in vertebrates. It includes a humoral and cellular component and differs from the innate immune system for the specific and memory-producing responses [1]. The proliferation of antibody-secreting plasma cells from specific antigen-stimulated B lymphocytes sustains the humoral component of the adaptive immune system, while T lymphocytes (i.e., helper, cytotoxic, and regulatory T cells) the cellular component. Among T cells, Th lymphocytes secrete cytokines and elaborate and prime the immune response, inducing immunoglobulin class switching of B cells and activation of cytotoxic T (Tc) cells and optimizing the bactericidal activity of phagocytes [1]. Th lymphocytes, characterized by expression of CD4 proteins, are activated when the MHC type II molecules expressed on antigen-presenting cells bind the specific T cell receptor. Th1 cells are regarded as “pro-inflammatory,” secreting cytokines (e.g., interferon- $\gamma$  and interleukin (IL)-12) and stimulating macrophage and cytotoxic T cell functions. Th2 cells secrete cytokines (e.g., IL-4 and IL-10) and have been associated with an “anti-inflammatory”

phenotype. Th cells also include the regulatory T cells (Treg) (that act to dampen the immune response) and the Th17 cells (that modulate neutrophil function) [1]. A shift from Th1 to Th2 cells (i.e., mainly induced by deregulated lymphocyte apoptosis) has been observed in the tardive stages of sepsis; the subsequent anti-inflammatory/immunosuppressive phenotype has been associated with secondary infections and death in septic patients [5]. Tc cells can induce death in somatic or tumor cells, after stimulation by MHC type I-related signaling, through the release of cytotoxins, perforin, and granulysin, the subsequent pores formation in the target cell membrane, the entrance of serine proteases, and thus the induction of apoptosis. Alternatively, Tc expression of Fas ligand can activate the extrinsic apoptotic cascade, inducing cell death [1].

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### 11.3 Effects of Sedative on Immune Responses

Most of the studies aimed at exploring the immunomodulatory effects associated with sedatives are unfortunately performed in a setting of the operating room. For this reason, most of the results presented in this review are mainly derived from clinical studies in which sedatives are used at hypnotic doses during general anesthesia.

Although only preliminary results are available, most of the studies aimed at exploring the immunomodulatory effects of sedatives suggest a predominant anti-inflammatory pattern associated with these agents, as well as an increased susceptibility to infection.  $\alpha 2$ -adrenoceptor agonists might be a possible exception to this generalization; indeed, these might be associated with an improved immune function and better outcomes, even in septic patients [1].

Several pathophysiological reasons might explain the effects of different sedatives. As example, as sleep deprivation may contribute to the immune dysfunction in critically ill patients [6], the sedative profile of the different agents may consistently have an immunomodulatory effect. Different from GABAergic agents (e.g., propofol or benzodiazepine) and opioids, which reduce the amount of non-rapid eye movement sleep, dexmedetomidine is associated with electroencephalographic and cerebral blood flow patterns similar to natural sleep [7, 8]. The improvement on the burden of sleep deprivation might explain the more favorable immune effect of dexmedetomidine in the ICU than other sedatives [1].

Another general indirect effect of sedatives on the immune system might be derived from the stimulation of the autonomic nervous system induced by different sedatives. In particular, the activation of the sympathetic nervous system (SNS) has been associated with immune dysfunction [9, 10]. In this context, the suppression of SNS activity by sympatholytic sedation (e.g.,  $\alpha 2$ -adrenoceptor agonist) may exert some advantages to the immune system [1]. Consistently, the sympathomimetic effects associated with ketamine use are associated with a profound immunosuppression [11]. In particular, sedative doses of ketamine affect the immunoregulatory activities of macrophages, neutrophils, and mast cells [12]. Furthermore, Ohta et al. have demonstrated that ketamine inhibits the dendritic cell production of IL-12 and

the T cell differentiation [12]. Finally, even a single preoperative administration of ketamine has been demonstrated enough to attenuate the production of pro-inflammatory cytokines from peripheral blood mononuclear cells and the proliferative response of mononuclear cells [11, 12]. However, as ketamine is rarely used for long-term sedation in the ICU, it will be not extensively discussed in this review. Beyond these general mechanisms, different effects on the immune system have been demonstrated for each specific sedative agent.

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## 11.4 Propofol

Propofol and midazolam have been probably the most common sedatives used for critical care sedation for an extended period of time [13]. Both exhibit natural anti-inflammatory/immunosuppressive effects in several in vitro and in vivo models and, if used for long-term sedation in critically ill patients, have been associated with a clinically relevant impairment of the immune response [13]. As example, a 4-h sedation with propofol may lead to reticuloendothelial system dysfunction, enhancing lung and spleen bacterial colonization in an animal model of infection [14]. Probably, the intralipid-based formulation may contribute to propofol-induced immunosuppression [13, 15]. All these effects are partially sustained by the propofol inhibition of macrophage and neutrophil functions; furthermore, it exhibits antioxidant properties both inhibiting in vitro generation of reactive oxygen species [15, 16] and reducing in vivo free radical generation in cardiac surgery in humans [17]. This antioxidant effect may contribute to the in vitro observation of neutrophil phagocytosis impairment for *Escherichia coli* and *Staphylococcus aureus* [18, 19]. This in vitro effect might be due to a reduced intracellular calcium concentration in neutrophils [16]. Interestingly, this phagocytosis impairment seems to be similar to that induced from other sedatives. In particular, ex vivo studies have observed no effects on propofol-induced impairment on *S. aureus* phagocytosis, both during sedation (compared with methohexital [20]) and anesthesia (compared with isoflurane [21]). Finally, a reduced hydrogen peroxide production from septic rat ex vivo neutrophils was also observed with propofol [22], as well as suppression of LPS-induced release of the chemotactic and activating factor IL-8 from isolated neutrophils [23].

Impairment on macrophage chemotaxis, oxidative burst, and phagocytosis of *E. coli* have thus all been reported during propofol administration [18, 24]; these effects may be related to the loss of mitochondrial membrane potential and reduction in macrophage ATP levels [24]. Furthermore, as propofol inhibits inducible nitric oxide synthase (iNOS) [25–27], it suppresses lipopolysaccharide (LPS)-induced nitric oxide formation [25–27] as well as nitric oxide-induced apoptosis in macrophages [25].

Although data at sedative dose are missing, propofol seems to preserve Th1/Th2 lymphocyte subsets at anesthetic dose [28]. Nevertheless, ex vivo studies suggest that propofol might entirely reduce proliferative lymphocyte responses in

critically ill patients [29]. In particular, it can inhibit lymphocyte potassium channels, attenuating lymphocyte activation and proliferation [30]. Furthermore, propofol may induce lymphocyte apoptosis but at high concentrations (beyond sedative purpose) [31].

Systemically, low-dose propofol attenuates the plasma increase of  $\text{TNF}\alpha$  and IL-6 levels when given immediately or 1 or 2 h after endotoxin administration [32, 33]. Interestingly, the lowest the dose of propofol administered, the lowest the cytokine attenuation observed. Although this effect might be generalizable for propofol sedation, most of the studies aimed at quantifying circulating inflammatory mediator reduction have never been tested at doses below 5 mg/kg/h [34]. Critically, at high doses (20 mg/kg/h), propofol impairs bacterial clearance from the lung and spleen in rabbits injected with *E. coli* in vivo (compared with ketamine) [14].

As a conclusion, although most of the data available on propofol-based sedation are only derived from anesthesia and surgical settings, significant in vitro and in vivo data suggest that propofol has anti-inflammatory effects due to impairment of the innate immune response. Scarce information are available on functional effects of propofol on the adaptive immune response. Propofol may have a therapeutic application for attenuation of sterile inflammation; however, in the presence of infection, the impaired bacteria clearance may prove a significant problem.

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## 11.5 Benzodiazepines

Similar to propofol, benzodiazepines are often used for critical care sedation and present an immunosuppressant profile [1]. Nevertheless, slight differences might be observed between these sedatives in several in vivo studies. In particular, 48 h of midazolam infusion has been associated with a more profound reduction of serum pro-inflammatory cytokine (IL-1b, IL-6, and  $\text{TNF}\alpha$ ) than propofol infusion in critically ill patients [35]. Furthermore, serum concentrations of IL-8 (i.e., neutrophil chemotactic factor, an important mediator of the immune reaction in the innate immune system response) decreased more pronouncedly in the midazolam group. Finally, the reduction in IL-2 serum concentrations and the increase in interferon-gamma levels were more relevant in the propofol group [35]. Thus, clinical data on critically ill patients support a greater anti-inflammatory/immunosuppressant potential for midazolam than for propofol.

Preclinical studies performed on animal models showed that the anti-inflammatory actions of benzodiazepines mainly involve the innate immune system and correlate with increasing mortality due to infections. As example, midazolam significantly inhibits LPS-induced upregulation of cyclooxygenase 2, inducible nitric oxide synthase in macrophages, NF-kB transcriptional activity, protein kinase, and superoxide production [36]. An impairment in macrophage oxidative burst and bacterial phagocytosis has also been demonstrated with midazolam in preclinical

studies [37]. Finally, benzodiazepines suppress LPS-induced TNF $\alpha$  activity in macrophages [38].

Conflicting results exist on benzodiazepine effects on neutrophil function; in particular, whereas some evidence suggests a neutrophil impairment induced by midazolam [37], an acute dose of diazepam seems to correlate with a pro-inflammatory effect, improving neutrophil function. Nevertheless, chronic diazepam assumption correlates with an immunodepressant effect [39, 40] with depression of polymorphonuclear cell phagocytosis, adherence, and chemotaxis [40]. Further in vitro studies suggest that benzodiazepines suppress neutrophil oxidative burst [41–43]; this effect was thus blocked by the peripheral benzodiazepine receptor antagonist PK 11195 [38].

Only preliminary results are available for benzodiazepine effects on lymphocyte functions. In particular, evidence from animal studies suggests that low-dose of benzodiazepines improves stimulated lymphocyte proliferation over the first weeks of treatment, whereas with longer treatment times, a decreased lymphocyte proliferation is observed, until impaired lymphocyte humoral responses following long-term (60 days or greater) treatment [39].

Preliminary data show that low-dose benzodiazepines impair *Salmonella typhimurium* clearance and, particularly for long-lasting treatment, increase mortality from this infection [39]. Furthermore, an in vivo study showed that, even with short-term treatment, benzodiazepines reduce resistance to systemic *Klebsiella pneumoniae*, increasing mortality [44]. Similarly, epidemiologic data have reported benzodiazepine use as a risk factor for complicated community-acquired lower respiratory tract infection [45].

As a conclusion, similar to propofol, benzodiazepines induce suppression of innate immune response probably through peripheral benzodiazepine receptor on immune cells [46]. An increased mortality rate due to infection correlates with impairment of the innate immune response; on the other hand, studies probing effects on adaptive immunity are needed.

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## 11.6 Opioids

Opioids are often used for critical care sedation to facilitate mechanical ventilation and improve the patient's comfort [1]. Several pieces of evidence suggest that opioids suppress innate and adaptive immune system [47, 48]. Nevertheless, most of the studies on this specific topic are focused on morphine use, and only few data are currently available on the suppressing effects of other opioids [1].

Morphine has been associated with in vitro anti-inflammatory effects; consistently, an increased mortality rate has been observed in several in vivo animal models of infection [49]. In particular, morphine treatment was associated with the worst outcome during *Streptococcus pneumoniae* [50, 51], *Salmonella typhimurium* [52], *Salmonella enterica* [53, 54], *Toxoplasma gondii* [55], or *Listeria monocytogenes* infections [56]. Furthermore, animals chronically treated with morphine spontaneously developed

infections with enteric bacteria, suggesting that opioid treatment may contribute to the translocation of gram-negative bacteria also in critically ill patients [57].

These effects might be correlated with morphine-induced inhibition of myeloid cell differentiation [58] and, generally, with the overall suppression of immune responses at the early stage of activation. In particular, morphine inhibits phagocytosis and macrophage activation [59, 60], chemotaxis [61, 62], and cytokine expression [63]. Furthermore, several studies suggest an opioid-induced inhibition of macrophage respiratory burst activity [64, 65] and induction of superoxide and NO formation [63, 66], leading to inappropriate macrophage apoptosis [1].

$\mu$ -Opioid receptors seem to be related to all these effects; indeed, specific  $\mu$ -antagonists reduce morphine's immunological effects, while  $\delta$ - or  $\kappa$ -antagonists had no effects [60, 67, 68]. Furthermore,  $\mu$ -opioid receptor gene deletion reduces opioid-related phagocytosis impairment [69, 70]. On the other hand, the anti-inflammatory effect leading to reduced TNF $\alpha$ , IL-1, and IL-6 production may involve  $\mu$ -receptors as well as other opioid receptors [48]. Although  $\mu$ -receptors on the macrophage and lymphocyte surface seem to be related to this effect, exact mechanisms of opioid-induced immunosuppression are not completely understood. Nevertheless, increasing evidence suggest also indirect mechanisms for opioid-induced immunosuppression involving the stimulation of the hypothalamic-pituitary axis and the SNS [47–49]. Interestingly,  $\alpha$ 2-adrenoceptor agonist, such as clonidine, ameliorated the immune effects of morphine withdrawal [71].

Opioids suppress NK cell activity both after acute and chronic administration [48], through an effect probably mediated from a CNS locus. In particular, opioid analogues unable to diffuse across the blood–brain barrier (e.g., N-methyl morphine) do not produce this NK cell activity inhibition [72].

Chronic opioid treatment reduces proliferation of thymocytes and T lymphocytes and induces an imbalance in the lymphocyte subsets, as well as in their function and apoptosis control [1]. In particular, treatment with morphine and fentanyl inhibits lymphocyte proliferation and increases cellular apoptosis [73, 74]. Similar to macrophages, lymphocytes seem to be induced to apoptosis through morphine-induced upregulation of Fas and caspase pathways [63, 66, 73, 75, 76]. Several authors suggest that lymphocyte apoptosis might be critical for septic pathogenesis, involving intrinsic and extrinsic apoptotic mechanisms [5] with subsequent caspase activation and sensitization to septic injury. However, it is unclear if these findings might be applicable also in critically ill septic patients in the ICU, particularly taking into consideration timing and dosing of opioids used for sedation in these patients. Most of these authors conclude that further studies focused on clarifying the effects of opioids on sepsis-induced apoptosis are urgently required [1].

Furthermore, chronic opioid treatment produces a shift from Th1 to Th2 lymphocyte subset, probably through intracellular (e.g., adenylyl-cyclase-mediated differentiation factors [77, 78]) and humoral mechanisms (e.g., opioid-induced inhibition of Th1 cytokines, IL-2, and IFN- $\gamma$  and concomitant increase of Th2 cytokines, IL-4, and IL-5 [77, 79]). Opioids also impair the transition from B cells to plasma cells through an  $\mu$  opioid receptor-mediated mechanism, further inhibiting the adaptive



immune response. Finally, morphine exposure also downregulates MHC class II expression, affecting antigen presentation [80].

As a conclusion, opioid's effects on macrophages and lymphocytes may have a critical importance in the ICU patients, leading to acquired suppression of both innate and adaptive immune systems. Particularly in critically ill patients, the opioid administration may therefore contribute to the immunosuppression and predisposition to infection and participate in sepsis pathogenesis.

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## 11.7 $\alpha$ 2-Adrenoreceptor Agonists

The SNS exerts immunosuppressive effects through direct stimulation of  $\alpha$ 1- and  $\beta$ -adrenoceptors on immune effectors. In particular, these receptors trigger signaling cascades that reduce the expression in the immune cells of pro-inflammatory cytokines increasing those with anti-inflammatory effects [81, 82] and contribute to lymphocyte apoptosis [83, 84]. Interestingly, stimulation of  $\alpha$ 2-adrenoceptors may induce both pro-inflammatory [85, 86] and anti-inflammatory responses [87–91], probably depending on the different peripheral and CNS actions of  $\alpha$ 2-adrenoceptor agonists. Peripherally,  $\alpha$ 2-adrenoceptors stimulate innate immunity and pro-inflammatory effects [92–94], while centrally the sympatholytic actions of  $\alpha$ 2-adrenoceptor agonists may reduce inflammation, shifting toward an anti-inflammatory phenotype [82, 95]. Furthermore, inflammation itself may modulate the effect of  $\alpha$ 2-adrenoceptor stimulation [96]; as example, dexmedetomidine administered during systemic inflammation may act in an anti- rather than pro-inflammatory manner [1]. As a consequence, a highly modulated pro-/anti-inflammatory response might be observed during  $\alpha$ 2-adrenoceptor agonist treatments. As example, in contrast to benzodiazepine and propofol effects,  $\alpha$ 2-adrenoceptor agonists increase in vivo macrophage phagocytosis, free radicals, superoxide, and NO-dependent killing of pathogens, such as *Mycobacterium avium* and *Toxoplasma gondii* [92–94]. Furthermore,  $\alpha$ 2-adrenoceptor agonists increase production of pro-inflammatory cytokines [92]; in particular, a dose-dependent TNF $\alpha$  production is observed in vitro with  $\alpha$ 2-adrenoceptor stimulation [85], as well as an in vitro IL-12 monocyte production that may stimulate cell-mediated and Th1 immune response [97]. Nevertheless, these pro-inflammatory effects might be counterpoised to anti-inflammatory effects observed in vivo in other studies in which dexmedetomidine attenuated ventilator-induced lung injury correlating with reduced local inflammatory responses [98].

At clinical doses, clonidine and dexmedetomidine do not affect chemotaxis, phagocytosis, and superoxide formation in human neutrophils [99]. Only few studies have explored the effects of  $\alpha$ 2-adrenoceptor agonists on lymphocytes. Nevertheless, similar to other sedatives and the opioids, a significant reduction of Th1 phenotype in T cell subsets has been observed during systemic inflammation [100]. However, a concomitant reduction in T regulatory cells has been also in vivo observed during sedation with dexmedetomidine. In particular, in a randomized

controlled trial on septic patients, Guo et al. concluded that dexmedetomidine might decrease the duration of immunosuppression in these patients, through a more rapid normalization of T regulatory cell count than propofol and midazolam [101]. Thus, in contrast to pro-inflammatory responses induced in macrophages in vitro, lymphocytic responses seem to shift to an anti-inflammatory (not immunosuppressive) phenotype in vivo [1].

Studies on humoral responses associated with dexmedetomidine infusion have demonstrated an intense anti-inflammatory effect in LPS-treated animals, with a significant reduction of TNF $\alpha$  and IL-6 circulating levels and with a significant improvement in mortality rate [87, 88]. Similarly, a significant reduction in pro-inflammatory cytokines has been observed in clinical studies on critically ill patients comparing dexmedetomidine vs. midazolam [89] and dexmedetomidine vs. propofol [90]. The difference between the pro-inflammatory effects exerted on cellular components of the innate immune system and systemic humoral effects (associated with reduced levels of pro-inflammatory cytokines) may be related to the  $\alpha$ 2-adrenoceptor agonist's different effects on the CNS and adaptive immune system [1, 95].

As a conclusion,  $\alpha$ 2-adrenoceptor agonists have complex interactions with the immune system, and patients may benefit from  $\alpha$ 2-adrenoceptor agonist sedation in many ways. In particular, dexmedetomidine presents humoral anti-inflammatory effects particularly during systemic inflammation, but it contemporaneously improves macrophage function and antiapoptotic activity for several immune cells [8, 102].

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## 11.8 Volatile Anesthetics

Although several evidences exist on immunological influences of halogenates, most of them are derived from studies using halogenates as general anesthetics, instead of sedative in the ICU. As example, a more reduced phagocytotic and microbicidal function has been described in vivo for alveolar macrophages during anesthesia with isoflurane than with propofol [103]. Nevertheless, a wide variation on humoral inflammatory pattern has been described for a similar group of patients; in particular, animal studies suggest that inhalation of isoflurane at anesthetic concentrations induces gene expression of pro-inflammatory cytokines in alveolar macrophages within 2 h [104]. Similarly, increasing gene expression of pro-inflammatory mediators, such as IL-1b, IL-8, interferon-gamma, and TNF $\alpha$ , has been observed in vivo during isoflurane administration than propofol infusion [105]. On the other hand, other studies have demonstrated a suppressed cytokine production in mechanically ventilated animals with lipopolysaccharide-induced lung inflammation during inhalation with halothane with respect to thiopentone administration [106]. In particular, a reduced polymorphonuclear cell recruitment and TNF $\alpha$  and IL-6 concentrations in bronchoalveolar lavage fluids have been observed in this model. Interestingly, this

halogenate-induced pro-inflammatory response in the lung was transient and reversed 20 h after anesthetic withdrawal [106]. The different effects induced by halogenates on humoral inflammatory pattern might partially be related to the specific halogenate drug used and on the concentration applied to the patient. The immunomodulatory effects of volatile anesthetics might thus differ from anesthesia in the operating room to sedation in the ICU.

In 2000 Goto et al. have *in vivo* demonstrated that sevoflurane does not influence the rate of neutrophil apoptosis, cytokine concentration, or neutrophil counts at clinical dose [107]. On the other hand, isoflurane has been demonstrated to reduce the phagocytic capacity of all polymorphonuclear cells [21].

Similarly, Welch et al. have reported that halothane reversibly inhibits human neutrophil bacterial killing function probably affecting the neutrophil oxidative microbicide activity [108]. Indeed, ROS production by activated neutrophils is inhibited by halothane, enflurane, isoflurane, and sevoflurane [109]. As inhibition of ROS release by volatile anesthetics results in the suppression of initial inflammatory responses, it might provide a therapeutically beneficial effect during condition caused by unbalanced inflammation, such as ventilator-induced lung injury or ischemia-reperfusion injury [109].

Also, the adaptive immune system is affected by halogenates. In particular, halothane, sevoflurane, isoflurane, and enflurane have been demonstrated to suppress the release of IL-1 and TNF $\alpha$  from human lymphocytes [110], reducing the immunocapacity of these cells against microorganisms and tumor cells. The exact mechanisms by which halogenates inhibit lymphocyte function are unclear; however, the caspase-mediated induction of lymphocyte apoptosis seems to have a role in this process [108]. Indeed, isoflurane and sevoflurane have been demonstrated to induce apoptosis in human lymphocytes in a dose-dependent and time-dependent manner [109, 111].

In conclusion, most reports conclude that halogenates may amplify inflammation more than propofol, particularly regarding cytokine gene expression. However, volatile anesthetics may hamper the bactericidal activity of alveolar macrophages more efficiently than propofol does. However, these inhibitory effects may contribute to anti-inflammatory responses, by regulating the secretion of pro-inflammatory cytokines implicated in the pathophysiology of systemic inflammation [25].

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## Conclusions

A predominant anti-inflammatory and immunosuppressive pattern has been associated with sedative use. Although these anti-inflammatory effects might be conceptually useful during uncontrolled systemic inflammatory response syndrome not associated with infections, the sedation-induced immunosuppression might increase susceptibility to microbial colonization and worsen the outcome of septic patients. In the future, consideration of the immune effects of sedatives may play a role in their selection among critically ill patients, and their use may be tailored toward therapeutic manipulation of the immune response (Table 11.1).

**Table 11.1** Immunomodulatory effects of sedatives

		Propofol	Benzodiazepines	Opioids	α2-Adrenoceptor agonists	Volatile
Innate	Reticuloendothelial	↓	N/A	↓	↑	N/A
	Neutrophil function	↓	↓	N/A	–	↓
	Macrophage phagocytosis	↓	↓	↓	↑	↓
	Macrophage oxidative burst	↓	↓	↓	↑	N/A
	Macrophage chemotaxis	↓	↓↓	↓	↑	N/A
Adaptive	Pro-inflammatory cytokines	↓	↓↓	↓	↑	↓ ↑ (Isoflurane)
	Lymphocyte apoptosis	↑	N/A	↑	↓	↑
	Lymphocyte proliferation	↓	↓	↓	↑	↓
	T subset ratio	–	N/A	↓	↓	N/A

Specific effects of sedatives on innate and adaptive immune systems, in terms of increase (↑), reduction (↓), or no effects (–)

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## 12.1 Introduction

Sleep is an active process related to complex biologic and environmental factors that have not been completely elucidated to date. There is evidence that sleep disturbances and deprivation, which occur frequently in critically ill patients, are associated with adverse outcomes [1, 2]. It has been demonstrated that sleep duration in intensive care unit (ICU) patients is shortened and fragmented [3]. Many patients treated in the ICU have disturbed sleep patterns, hallucinations, and delirium. Sleep is essential for restoring energy and equilibrating the mind. Sleep deprivation alters cognition, leading to apathy, confusion, and delirium, all of which may increase morbidity and mortality [4]. Sleep deprivation also has detrimental effects on the immune system, impairing resistance to infection and wound healing [5].

A number of environmental (clinical and nonclinical) factors contribute to sleep disturbances. Clinical factors include mechanical ventilation, drainage positioning and maintenance, bronchial aspiration, hygiene, nursing care, and many other procedures that require pain, stress, and psychological management. Nonclinical factors include disturbing noises from nursing and medical staff, other patients, and abnormal lighting.

As a consequence, sedatives are commonly given to critically ill patients to facilitate treatment, increase comfort, and promote sleep. The latter is a fundamental reason for

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sedative administration in critically ill patients, although physiological sleep and sedation may differ significantly as the relationship between sleep and sedation is extremely complex. For instance, sedatives and analgesics, which in certain circumstances may improve sleep, have been demonstrated to interfere with physiological sleep.

The present chapter will review the physiology of sleep, the effects of sleep deprivation during and after ICU stay, and strategies to promote sleep in critically ill patients.

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## 12.2 Sleep and Sleep Architecture

The basic organization of normal sleep includes two types of pattern: (1) non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep, in turn, includes four distinct stages (1–4) in a continuum of sleep depth, although the American Academy of Sleep Medicine (<http://www.aasmnet.org>) no longer recognizes three stages. NREM sleep stages 1–3 are referred to as N1, N2, and N3, with N3 reflecting slow-wave sleep (SWS), while REM is referred to as stage R [5]. Electroencephalographic (EEG) recordings have studied sleep cycles and stages. During a given sleep period, NREM and REM sleep alternate cyclically. Irregular cycling and/or absent alternations are associated with sleep disorders.

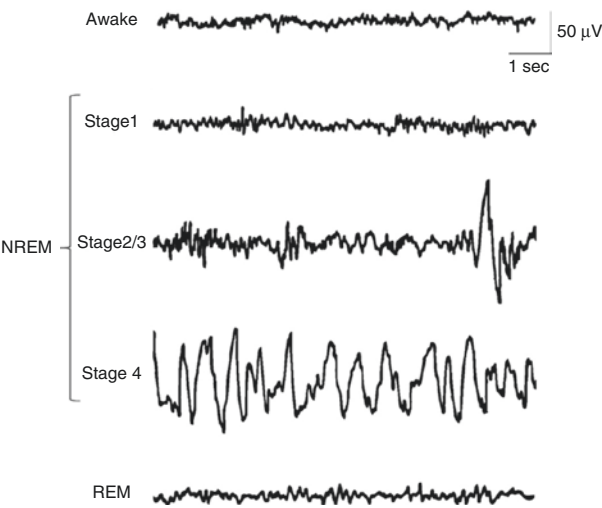
Physiologically, NREM constitutes between 75 and 80% of total sleep time (TST) [2]. N1 is a transition between wakefulness and deep sleep that is characterized by physical drowsiness combined with decreased ocular movements and a reduction in muscle activity. N2, in which the individual becomes unaware of their surroundings, is the predominant stage of the NREM phase (45–55%) [2]. N3 (SWS stage) is thought to be an anabolic and physically restorative stage. This is the deepest and most restful stage of the sleep cycle in which metabolic activity is at its lowest, leading to a reduction in oxygen consumption and growth hormone that in turn promotes protein synthesis, tissue healing, and physical recovery [2]. Conversely, during the R phase, which is associated with dreaming, cerebral and physiological activity are increased, and the brain's metabolic rate is similar to that of a waking state [2]. During the night, individuals cycle from NREM (75–80%) to REM (20–25%). While REM is a restful part of the cycle, it has a lower threshold for awakening than SWS or the deep sleep stages.

Detailed information on EEG patterns and sleep cycles are beyond the aim of the present chapter, and the reader is referred to the cited texts for further information. Table 12.1 and Fig. 12.1 summarize the main characteristics of the different sleep stages.

As temporal phenomenon, sleep is regulated by homeostatic and circadian processes that include continuous communication between the central nervous system, tissues, and organs. The circadian rhythm, regulated by the suprachiasmatic nucleus located in the hypothalamus, regulates the transition from wakefulness to sleep [5]. Homeostasis results from this balanced physiologic process.

**Table 12.1** EEG patterns characteristic of the NREM and REM stages [5, 22]

NREM—stage 1 (N1)	Transitions from wakefulness (marked by rhythmic alpha waves) to sleep. Characterized by replacement of the waking alpha EEG pattern by a low-voltage mixed-frequency pattern. It is the lightest stage of sleep and typically occupies 3–8% of the night
NREM—stage 2 (N2)	Characterized by a slowing of EEG frequency and an increase in EEG amplitude. Relatively low-voltage, mixed-frequency activity characterized by the presence of “sleep spindles” and “K-complexes.” Typically accounts for 40–55% of total sleep time
NREM—stage 3 (N3)	Transition to an EEG with high-amplitude delta waves, EEG waves with a frequency of 0.5–2 Hz and amplitude of at least 75 mV. Referred to as slow-wave sleep (SWS). The EEG shows increased high-voltage, slow-wave activity. An increased amount of high-voltage, slow-wave activity on the EEG is characteristic of stage 4. Accounts for 20% of total sleep time in young adults
REM stage (R)	The EEG resembles wakefulness in many ways, but muscle activity is greatly reduced. Desynchronized (low-voltage, mixed-frequency) brain wave activity, muscle atonia, and bursts of rapid eye movements. “Sawtooth” wave forms, theta activity (3–7 counts per second), and slow alpha activity also characterize REM sleep. Occupies 20–25% of total sleep time. REM sleep is associated with the greatest instability of respiratory and cardiac function during the night



**Fig. 12.1** Electroencephalographic patterns of sleep stages

### 12.3 Instrumental Analysis of Sleep Quality and Quantity

Polysomnography (PSG) is the standard tool used for measuring sleep [6]. EEG, electromyography, and electrooculography are measured and collected for the study period in question. Cardiorespiratory data (e.g., expiration, end-tidal CO<sub>2</sub>, and oxygen saturation) and other physiologic data (e.g., gastric pH) may also be collected

for evaluation. The need for skilled technicians makes PSG a costly process not always appropriate to ICU patients [7]. Bispectral index (BIS) analysis, which is designed to provide an EEG correlation with the human behaviors associated with general anesthesia, has been used as an alternative way to assess sleep in the ICU [8] (see Chap. 5). By means of frontal EEG waves, BIS shows the shift from wakeful low-voltage, high-frequency EEG patterns (alpha, beta) to the high-voltage, low-frequency component (theta, delta) of anesthesia or SWS [8, 9]. The BIS algorithm analyzes the EEG data and delivers a numerical value (0–100) that represents a degree of consciousness that correlates to estimated sleep depth. Although potentially useful, the role of so-called processed EEG monitors (*p*EEG) has not been clearly identified in ICU patients [7].

Actigraphy, a more recent tool for exploring sleep, identifies body movements via an internal accelerometer and calculates sleep time using a proprietary algorithm. The automated watch placed on the subject's wrist or ankle [10] has shown significant correlations and agreements with PSG [11]. While its primary use in clinical practice is the assessment of circadian rhythms outside ICUs, actigraphy has been used to measure sedation/agitation in the ICU, showing a good correlation with nurse-directed observation of agitation and sleep [12, 13].

Alternatives to instrumental evaluations include patient's self-report questionnaires (e.g., Richards–Campbell Sleep Questionnaire (RCSQ)) that have been applied in ICU patients to assess sleep quality. A brief questionnaire made up of five points, the RCSQ uses a visual analog scale to assess sleep depth, latency, awakenings, percentage of time awake, and quality of sleep [1]. However, patients' self-reporting may be influenced by the use of sedation and the presence of delirium.

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## 12.4 Causes of Sleep Deprivation in the ICU

The principal causes of sleep deprivation, disturbance, and fragmentation belong to different components of care and “life” in the ICU.

Mechanical ventilation is a major obstacle to physiological sleep in ICU patients, especially in cases of patient–ventilator asynchronies, central apneas due to over-ventilation, and inadequate ventilatory settings leading to increased respiratory efforts [14, 15]. Use of the appropriate ventilator mode and settings may have a strong impact on sleep quality. Similarly, the use of alarms may contribute to sleep disruption [16]. Polysomnography has shown that both intubated patients and those in noninvasive ventilation, delivered for over 24 h, experience major sleep disturbances [17]. Moreover, circadian sleep cycle disruption and shorter REM sleep have been associated with subsequent delirium and late noninvasive ventilation failure [6, 17].

Environmental issues are of primary importance to sleep quality and quantity in the ICU. Assistance from healthcare teams in monitoring, procedures, and assessments commonly contributes to sleep interruption (e.g., laboratory draws or chest x-rays for morning rounds). Moreover, nurse's activities frequently require a well-lit environment, and these inevitably generate noise that may further “disturb” patients'



sleep [18]. Specifically, the World Health Organization's guidelines on community noise recommend noise levels not exceeding 35 dB during the night and 40 dB during the day [<http://whqlibdoc.who.int/hq/1999/a68672.pdf>] [18, 19]. Noise pollution has a multifactorial origin, including alarms from infusion pumps, mechanical ventilators, and hemodynamic monitors. Healthcare staff themselves may be responsible for around 80% of the noise produced within the ICU [5, 20, 21].

Along with uncontrolled noise intensity, environmental light is another critical aspect of the human sleep–wake cycle. A high variability in lux intensity has been described in the literature [22, 23]. Moreover, and unlike for noise, there are no existing recommendations regarding the levels of light that should be respected in the hospital setting [23].

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## 12.5 Critical Illness, Sleep, and Sleep Deprivation in the ICU

The profound alterations in pathophysiology induced by illness cause sleep architecture in the ICU to change according to its day- and nighttime distribution, the percentage of time spent sleeping, and variations in distribution across the stages. Sleep is classically fragmented, especially in patients under mechanical ventilation [24–26]. Some studies have shown that while the total number of hours spent asleep may be around the correct amount over a given 24-h period, these are abnormally distributed across a series of short periods throughout the day and night [25, 26]. Light sleep frequently represents the dominant stages (N1 and N2), interrupted by frequent periods of wakefulness, while a relatively small percentage of time is taken up by the deep states (SWS or stages N3 and REM) [5, 27]. In addition, it has been demonstrated by the Basic Nordic Sleep Questionnaire (with two additional questions)—a tool designed to estimate the quality of sleep—that 50% of respondents have a clear recall of sleep disturbances, with sleep disorders lasting 6–12 months after ICU discharge in one-third of cases (see below) [28]. Moreover, it has been demonstrated that sleep deprivation and fragmentation during ICU stay correlate with either additional morbidity or mortality [22, 29]. The beneficial effects of sleep and the strong regulatory influence of the circadian system on immune functions have gained increased acceptance [30]. For instance, more undifferentiated naïve T cells and pro-inflammatory cytokines are released during early nocturnal sleep, whereas daytime wakefulness is the peak release time for circulating numbers of immune cells with immediate effects or functions (e.g., natural killer), as well as anti-inflammatory cytokine [30]. Due to the connections between the central nervous system and the immune system, as well as the direct innervation of the immune system by the autonomic nervous system, sleep has a strong influence in initiating effective adaptive immune responses that eventually produce a long-lasting immunological memory [5, 30]. Prolonged sleep deprivation/fragmentation, allied to the coexisting stress response, may thus invoke a sustained cytokine imbalance, leading to a chronic inflammatory condition and immunodeficiency (see also Chaps. 1 and 10) [5, 30]. In addition to direct and indirect immune dysregulatory effects, the neuroendocrine stress system is profoundly affected. Sleep deprivation may reduce body temperature

and weight, despite increased energy expenditure [31]. Similarly, there may be an increase in insulin resistance [32]. Sleep-deprived patients have also demonstrated decreased glucose tolerance, insulin resistance, lower thyrotropin, and elevated evening cortisol levels [33]. Sleep deprivation has equally been shown to induce the onset of a catabolic state (increase in urinary nitrogen elimination) [34]. Finally, sleep-deprived patients display higher oxygen consumption, CO<sub>2</sub> production, heart rate, and catecholamine levels [35], all of which are characteristics of a stress response. Respiratory function may be also impaired, and there is a risk of reduced ventilatory response to hypercapnia and hypoxemia, reduced inspiratory muscle endurance (reduced product of inspiratory muscle load and sustained time), and decreased central motor output to the upper airway muscles in response to hypercapnia [5]. All these conditions may be obstacles to respiratory weaning in patients undergoing prolonged mechanical ventilation. Correlations between sleep deprivation and delirium have been identified [17], and medications used to control the delirium that affects up to 50% of critically ill patients may also have a negative effect on sleep quality and quantity, further increasing the risk of delirium [5, 36, 37]. Subclinical alterations in sleep–wake states potentially reflecting a form of brain dysfunction contributing to delirium emergence have been identified using combined EEG spectral analysis and visual quantitative EEG analysis [6]. In light of this, procedures aimed at improving sleep have been associated with improved clinical outcomes, specifically, an important reduction in ICU delirium [18, 38].

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## 12.6 How to Promote Sleep in the ICU

Efforts should be made to promote sleep and respect the sleep–wake cycle by optimizing patient comfort, continuously assessing and treating pain and anxiety, and addressing all other environmental factors that contribute to sleep disruption in the ICU [39]. The Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit published in 2013 “recommend promoting sleep in adult ICU patients by optimizing patients’ environments, using strategies to control light and noise, clustering patient care activities, and decreasing stimuli at night to protect patients’ sleep cycles” [39]. The following interventions are necessary to achieve this goal: controlling noise and light, applying appropriate pharmacological interventions, and providing uninterrupted sleep periods, psychological support, ventilator synchrony, effective pain therapy, relaxation techniques, and music therapy (recipients of music therapy seem to have better sleep scores) [5, 39, 40].

### 12.6.1 Use of Sedatives: Lights and Shadows

Sedatives are commonly given to critically ill patients to facilitate their treatment, increase comfort, and promote sleep. However, these medications, while useful, can negatively affect sleep by promoting drug withdrawal syndrome and/or delirium [5].

Sleep is an essential biologic function that is easily reversed by external stimuli. As mentioned above, physiological sleep is characterized by circadian cycles and a progression across sleep stages. Sedation, conversely, does not possess these features. EEG analysis during sedation shows only medication-specific and dose-dependent effects. The differences between natural sleep and pharmacological sedation are hence key factors. Sedation—a nonphysiological condition induced by drugs—most commonly acts on the following  $\gamma$ -aminobutyric acid (GABA) receptors that make up the endogenous sleep pathway in the central nervous system:

- Benzodiazepines (BDZs) and propofol (PRO) are common first-line interventions when sedation is necessary in the ICU [39, 41]. BDZs activate the  $\alpha$ -1-GABA<sub>A</sub> receptor subunit activating the inhibitory system [42]. At higher doses, BDZs affect more generalized areas. At low doses, BDZs and PRO suppress SWS and may decrease REM sleep [43]. Both drugs may shorten sleep latency and increase N2 sleep. At higher doses, a characteristic slowing of EEG is produced. A burst suppression pattern, similar to a comatose pattern, can develop, and N3 sleep may be abolished when this is repeated [5, 44]. PRO is believed to act on the GABA<sub>A</sub> receptor in a different site to BDZs. At the level of sedation required in critically ill patients, propofol has been shown to worsen their already impaired sleep quality [45].
- A sedative medication that has recently gained great popularity for light sedation and sleep promotion is dexmedetomidine (DEX), an  $\alpha$ -agonist [46–48]. DEX has a different relationship with sleep than GABA agonist sedatives. The beneficial effects of DEX on delirium include its high selectivity for  $\alpha$ 2-adrenoceptors, its lack of anticholinergic effects, and its promotion of a physiological sleep-like state that reduces requirements for other agents with greater potential for delirium (e.g., opioids and GABAergic agents) [49, 50]. DEX induces sleep by acting on the locus coeruleus, where it decreases the firing of noradrenergic neurons and activates endogenous NREM sleep by promoting pathways (disinhibition of the ventrolateral preoptic area) [49, 51]. As such, DEX produces a state closely resembling physiological N2 sleep [52]. EEG shows a dose-dependent slowing, a decrease in REM stages, an increase in SWS, and an increase in the N2 stage (based on increases in spindle activity very similar to those observed during natural sleep, but with longer duration) [52]. Similarly, functional magnetic resonance imaging has demonstrated analogies between sedation with DEX and physiological sleep [53]. Importantly, patients sedated with DEX appear very similar to those under physiological sleep (easily aroused and more cognitively intact upon waking) than those whose sleep is induced by GABA agonists [54]. These similarities with natural sleep are probably due to DEX's interaction with physiological sleep pathways (far from GABA agonists' site of action). A randomized controlled trial of 61 ICU patients (age  $\geq$  65 years) after non-cardiac surgery (not requiring mechanical ventilation) was recently carried out. Patients receiving DEX (0.1  $\mu$ g/kg/h;  $n$  = 31) showed an increase in the N2 sleep stage (43.5%) compared with those receiving a placebo (15.8%);  $P$  = 0.048). In

addition, total sleep time was prolonged, with a decrease in the percentage of the N1 stage, increased sleep efficiency, and improved subjective sleep quality [47].

- Opioids are commonly administered to critically ill patients to treat pain and improve comfort. As pain may be the most significant impediment to sleep, it is logical that opioids may improve sleep [55]. However, opioids are only occasionally titrated for their sedative effects. Sedative/hypnotic effects are attained by interacting with the ponto-thalamic arousal pathway, exerting a dose-dependent REM-suppressive effect (mediated by mu receptors) [5, 42, 56].
- Antipsychotics are frequently administered to critically ill patients to treat agitation and delirium [39, 41]. Moreover, haloperidol has been shown to increase sleep efficiency and the N2 stage, with minimal effects on slow-wave activity and REM sleep [5]. Similarly, atypical antipsychotics (e.g., olanzapine and risperidone) may increase the total sleep time and SWS that have been correlated with subjective sleep quality [57, 58].
- Finally, melatonin (and melatonin receptor agonists) may help to promote sleep. To date, however, the only evidence of this is a single-center randomized controlled trial showing a reduction in delirium in less severely ill (i.e., not mechanically ventilated) elderly ICU population [59]. Therefore, while melatonin and related agonists may have benefits, these cannot be universally recommended without further data.

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## 12.7 After ICU Discharge

It has been observed that poor sleep quality, quantity, and architecture may remain profoundly altered after discharge from the ICU following an acute illness [60, 61]. A study examining factors associated with the psychological outcomes of former ICU patients showed that up to 50% have self-reported sleep problems 1 week after hospital discharge [61]. Although sleep quality improved over time in nearly one-third of cases, moderate to severe problems were observed after 6 months and independently associated with poor psychological recovery [1, 62]. However, the precise causes of these sleep alterations remain unclear. It is possible that the medical problems of patients discharged from the ICU may not be fully resolved, with sleep disturbances an ongoing symptom. It may also be that acute illness, environmental disturbances, exposure to multiple medications affecting the nervous system, and more general “invasive” care cause new sleep disturbances independent to the basic illness. In this sense, sleep disturbance may be considered similar to other cognitive dysfunction that develops following ICU stay.

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### Conclusions

Critically ill patients are susceptible to severe sleep deprivation, the consequences of which include ventilatory weaning failure, hormonal imbalance, metabolism alterations, neurocognition defects, delirium, and immune impairments. The causes are clearly multifactorial, including the patient’s illness, medications, medical and nurse assistance, and a host of environmental

disturbances. The relationship between poor sleep in critically ill patients and their ultimate outcomes remains partially unknown. However, sleep disturbances have been shown to contribute to the critical issue of brain dysfunction during and after ICU stay. Clinical guidelines therefore strongly support and recommend the application of a multimodal approach aimed at preserving the wake–sleep cycle. While there is no perfect medication—the so-called magic bullet—that will consistently guarantee physiologic-like sleep, a multimodal approach taking account of light, noise, ventilation modes, analgesia, the most appropriate and effective sedatives, and nurse care may help improve sleep patterns in critically ill patients [62].

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## 13.1 Delirium Terminology

The term delirium derives from the Latin verb “delirare,” which literally means “to go out of the groove.” In fact, “de” means to be away and “lira” means furrow, giving the idea of a maniac plowing a field with no rationale plan. The first report of a disease similar to delirium is the one given by the ancient Greek physician and philosopher Hippocrates (460 B.C–371 B.C), who introduced the word “phrenitis” to describe a disease characterized by fluctuating disorientation and agitation. Nevertheless, it is with Celsus and other Roman writers that the term delirium was used interchangeably with the word “phrenitis,” to indicate a disease-associated temporary change in mental status characterized by agitation, and the word “lethargus” in case of confusion associated with drowsiness. Nowadays, the term delirium is still underused in clinical settings. Instead, terms such as ICU psychosis, ICU syndrome, acute confusional state, septic encephalopathy, acute brain failure, depression, dementia, etc., have often been used in ICU as synonyms, frequently meaning very different entities [1]. This confusion in terminology could partially be responsible for the low detection rate of delirium among ICU physicians, who recognize less than half of the cases of this condition [2].

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## 13.2 Defining and Identifying Delirium

Early diagnosis of delirium is of paramount importance [3–7]. Unfortunately, there are no instrumental diagnostic means to detect delirium, which therefore remains a clinical diagnosis. Delirium is not a disease but a syndrome with a wide spectrum of possible aetiologies [8]. Its presentation may also be variable. In fact, it may present itself in hyperactive, hypoactive, or mixed forms. Although it is a common belief that the hyperactive—characterized by agitation, restlessness, and emotional lability—is the most frequent presentation of delirium, this is not true since it accounts for just 1.6% of the cases. Instead, hypoactive delirium—characterized by decreased responsiveness, withdrawal, and apathy—and mixed forms are far more frequent, accounting for 43.5% and 54.1%, respectively [9]. The prognosis seems to be worse with hypoactive delirium, possibly due to relative underdiagnosis and consequently delayed treatment [10]. In addition, there is a particular type, the so-called subsyndromal delirium, which presents one or more symptoms of delirium that never progresses to a full diagnosis. It is associated anyway with a worse outcome [11].

Delirium presents an acute or subacute onset of altered cognition or a disturbance in perception that is not better attributable to a preexisting dementia. It typically involves a reduced capability of focusing and maintaining attention and may or may not include delusions [12]. Reference standards for the diagnosis of delirium are the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) [13] and the tenth revision of the *International Statistical Classification of Diseases and Related Health Problems* [14]. However, these diagnostic criteria need extensive training to be applied in clinical practice [15]. In fact, ICU staff typically do not recognize delirium in almost three quarters of patients who have this condition. Instead, proper screening by trained nurses were able to identify delirium in up to 64% of patients, previously judged to be delirious by a psychiatrist, a geriatrician, or a neurologist [16].

In order to facilitate the diagnosis of delirium by non-psychiatrists, some different tools have been developed. In particular, two scales are useful and commonly utilized in the intensive care unit setting: the Intensive Care Delirium Screening Checklist (ICDSC) [17] and the Confusion Assessment Method for the ICU (CAM-ICU) [18] (Table 13.1). Although such scales are fundamental in objectively diagnosing delirium for research purposes, their sensitivity is a matter of debate. Some studies have shown a high sensitivity when such assessments were performed by bedside nurses [19], whereas other studies have shown conflicting results [20]. Used without a sedation scale, both the scales do not differentiate hyperactive from hypoactive delirium and do not quantify the relative importance of individual elements. Moreover, these tools identify delirium the presence or the absence of delirium, although it is clear the severity of delirium can differ. Despite these limitations, the CAM-ICU and ICDSC are currently the two accepted methods for identifying delirium in ICU [21].

**Table 13.1** Scoring systems for the diagnosis of delirium in critically ill patients

System, Scoring Method, and Criteria Confusion Assessment Method for the ICU (CAM-ICU)		
1. An acute change from mental status at base line or fluctuating mental status during the past 24 hr		
and		
2. Inattention		
Evaluated by an Attention Screening Examination (ASE):		
1: AUDITORY (pt. must squeeze the operator hand when a random letter A is pronounced ex. SAVEHAART)		
2: VISUAL (5 pictures among 10 are the same: pt. must recognize it)		
Test is positive if more than two errors		
and		
4. Disorganized thinking		3. Altered level of consciousness
or		
Asking 4 yes or no questions having the patient follow a simple command. Positive if more than 1 error		Positive if RASS ≠ 0
= DELIRIUM		

13.3 Relevance of the Problem

As showed by the American Association of Retired Persons, delirium is one of six leading causes of injuries associated with hospitalization in patients over 65 years of age [22]. The incidence of delirium is difficult to determine. In ICU, 20–50% of lower severity patients or those not receiving mechanical ventilation experience at least one episode of delirium during their stay. In those receiving mechanical ventilation, the incidence increases, reaching 80% [18]. Populations with variable severity of illness and under-recognition of the syndrome can in part explain this broad range in incidence figures [23, 24].

Delirium is often seen as a temporary attenuation of brain function, usually followed by a full remission. However, strong evidence exists that delirium augments risk of intubation by three times and predicts additional ten days in the hospital, each day of delirium increasing the risk of a prolonged hospital stay by 20% [25]. Similarly, Salluh et al. [26], found that, even after correcting for variables such as age, sex and Apache II, critically ill patients with delirium had an increased mean length of stay and increased mean duration of mechanical ventilation (almost 2 days longer than patients without delirium). In addition, delirium is associated with a higher ICU and in-hospital mortality in both the short term and the long term. As demonstrated by Ely et al. [27] in mechanical ventilated patients, the probability of survival at 6 months shows a threefold decrease in those patients who developed

delirium. In addition, researchers found an increased risk of death after delirium in different postoperative populations, in elective and emergency surgery [28].

As regards cognitive sequelae, patients who manifest delirium during hospitalization are at higher risk of developing short-term (months) and long-term (>12 months) cognitive impairment, with memory, attention, and executive function problems [29–31]. Moreover, the duration of delirium is directly related to the development of cognitive impairment [29, 32]. Some investigators found an increased incidence of dementia up to 5 years after postoperative delirium (POD) [33]. In addition, delirium has been associated with post-traumatic stress disorder 3 months after surgery [34]. In addition, these patients have an increased level of care dependency or limitations in basic activities of daily living up to 12 months, which in turn increases their risk of institutionalization and decreases their quality of life [4, 6, 35–40]. Unsurprisingly, this condition is responsible for an increase in hospital and ICU costs [41]. From what we discussed above, it is evident that delirium in the critically ill imposes a large burden on individuals and society. Therefore, monitoring for delirium in ICU prevention and treatment of this condition become fundamental issues.

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### 13.4 Risk Factors

The risk of developing delirium can be seen as the product of predisposing and precipitating factors, the first ones being those related to the patient (i.e., intrinsic vulnerability) and the second those which can act as triggers [42]. Although predisposing factors are present before ICU admission and are difficult to modify, precipitating factors occur during the course of critical illness. They may involve factors of the acute illness itself or be iatrogenic; these latter are potentially modifiable by preventive or therapeutic intervention.

With regard to predisposing factors, in many trials advanced age resulted in an increased risk of delirium [43–49]. However, although chronological age plays a role in predisposing to delirium, it probably acts as a surrogate variable for the accumulation of age-related risk factors that are differentially expressed among individuals. It is almost certainly the sum of these risk factors that is most important in determining the probability of delirium [50]. Another factor that strongly predisposes to delirium in hospitalized patients is alcohol abuse regardless of other existing conditions [51]. Comorbidities, such as respiratory, cerebrovascular including stroke, cardiovascular, and peripheral vascular diseases, diabetes, anemia, Parkinson's disease, depression, chronic pain and anxiety disorders [37, 52, 53], vision or hearing impairment, severity of illness on admission, smoking history, and drug use may also predispose patients to delirium [28, 35]. In particular, in the case of “multimorbidity,” i.e., a situation in which clinical patterns, evolution, and treatment become more complicated than the simple sum of the different illnesses, the capability to cope with stress is reduced and global vulnerability, including the risk for delirium [50], is increased.

Functional status, often regarded as the sixth vital sign, is defined as the sum of capabilities required (including social and cognitive functions) to perform daily activities such as dressing, cooking, washing, taking care of oneself, etc. [54]. Recently, many studies have shown an association of poor functional status with a series of postoperative complications such as wound infection and increased mortality, including delirium [40, 55]. The term “frailty” indicates a condition in which a critically reduced functional reserve due to multiple organ dysfunction limits the patient’s ability to cope with stressors and therefore predisposes to loss of physiological homeostasis [56]. Frailty has been demonstrated to be a predisposing factor for the development of delirium in the elderly who have undergone surgery [57–59].

Regarding precipitating factors, many illness-related conditions such as acidosis, anemia, fever, infection, sepsis, hypotension, metabolic imbalances such as hyper-/hyponatremia, acidosis, hyperbilirubinemia, and hyperazotemia can trigger delirium [37, 53, 60]. Patients often wake up in the unfamiliar surroundings of the ICU with no recollection of the previous days or even weeks, and this can be extremely confusing for them. In the perioperative period, preoperative fluid fasting and dehydration [61] can also increase the risk of developing delirium. Moreover, iatrogenic factors such as immobilization (i.e., catheters and restraints), medications (i.e., opioids, benzodiazepines), and sleep disturbances may also increase the risk. In particular, the latter two are extremely frequent in most of the critically ill patients and are potentially susceptible to modification. They are examined in detail below.

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### 13.5 Sedative and Analgesic Medications

Patients in Intensive Care Unit routinely receive sedative and analgesic medications to reduce anxiety and pain. These medications, however, are not without harmful effects. For example, continuous intravenous sedation is associated with prolonged mechanical ventilation as compared with sedation via intermittent boluses [62].

The existence of an association between delirium and exposure to sedative and analgesic medications is well known. In a combined surgical/medical ICU study, researchers demonstrated morphine as the strongest predictor of delirium [63]. Ouimet and colleagues [64] determined that coma-inducing sedatives and analgesics were associated with delirium with an odds ratio (OR) of 3.2 (95% confidence interval [CI] = 1.5–6.8). Marcantonio and coworkers [65] reported that benzodiazepines increased the risk of postoperative delirium in the study population in comparison to patients who were not receiving benzodiazepines (OR = 2.7, 95% CI = 1.3–5.5). In a study by Pandharipande and colleagues [66], lorazepam was an independent risk factor for daily transition to delirium (OR = 1.2, 95% CI = 1.2–1.4) in a dose-related way. Although studies have consistently identified lorazepam and midazolam as risk factors for delirium, the data regarding opioids is contradictory, since untreated pain does represent itself a risk factor for delirium. For example, Ouimet and coworkers [64] found that in ICU patients mean daily opioid doses

were lower among patients with delirium than among those without delirium. Similarly, in 541 hip fracture patients, Morrison and colleagues [67] determined that those treated liberally with opioid analgesics (>10 mg/day parenteral morphine sulfate equivalent) were less likely to develop delirium than patients who received less analgesia. Treatment with meperidine was an exception since this drug increased the risk for delirium as compared with other opioids [66]. More recently, apart from pain, studies have found an association between these drugs and delirium in at risk population [68–70]. Therefore, it is advisable to use these drugs judiciously and to provide adequate analgesia especially in the critically ill.

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### 13.6 Sleep Disturbances

Critically ill patients uniformly suffer from sleep disruption. Typically, the sleep of a critically ill patient is characterized by a predominance of waking state and light sleep (sleep stages II and I). Instead, there is a relative lack of rapid eye movement (REM) and deep sleep (delta sleep, formerly referred to as non-REM sleep stages III/IV) [71–74]. Multiple reasons are responsible for sleep disturbances in ICU: underlying disease, mechanical ventilation, pain, drugs, and a hard environment (noise, lights, lab draws, vital sign, invasive procedures, etc.) [75]. There is no doubt that a relationship between delirium and sleep disturbances do exists. Central components of delirium—that is, inattention, fluctuating mental status, and cognitive dysfunction—are also characteristic of patients with sleep deprivation. Nevertheless, even if sleep deprivation is plausible as a contributing factor in the onset of delirium, data definitively establishing it as an independent risk factor is still lacking [76]. Sleep interventions—i.e., promoting natural sleep, use of ear plug, limit lights and noise at night, etc.—may be a promising approach for improving delirium-related outcomes, although bias issues, varying methodologies, and multiple confounders make it difficult to draw any conclusion on this strategy. Further systematic studies are needed in order verifying the link between sleep interventions and delirium-related outcomes [77]. For further information, the reader is referred to the dedicated Chap. 11.

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### 13.7 Pathophysiology

Given the individual and social impact of delirium in terms of short- and long-term complications, a treatment based on solid pathophysiological bases would be largely desirable. Unfortunately, despite important advancements in neuroimaging, pathophysiology of delirium remains poorly understood. Several theories have been proposed to explain pathophysiology of delirium. Difficulty in outlining a definitive theory is partially due to the complex interplay between delirium and the baseline illness. The detailed analysis of all these theories is beyond the purpose of this chapter. Here, we report synthesis of the main mechanisms



involved in the genesis of delirium: inflammation, decreased cerebral blood flow, and neurotransmitter imbalance.

### 13.7.1 Inflammation

Inflammation has a strong association with the development of delirium in sepsis. A recent multicenter trial [78] estimated encephalopathy associated with sepsis with a prevalence of 32.3%. It is often believed that delirium in sepsis is mediated by inflammatory cytokines and endotoxin [79]. Studies demonstrated an increased incidence of delirium in septic patients with higher systemic inflammatory markers such as C-reactive protein, cortisol, and interleukin 8 (IL-8) [80, 81]. Researchers demonstrated that inflammatory mediators are able to activate microglia, which has a role in maintaining neuronal population's homeostasis by the phagocytic clearance of dysfunctional neurons. However, activation of microglia can lead to increased tissue levels of nitric oxide and reactive oxygen species, determining the onset of a self-maintaining loop between tissue damage and inflammation. As a result, damage of the blood-brain barrier (BBB), alterations in cerebral blood flow (CBF), endothelial dysfunction as well as changes in neurotransmitter levels can occur, leading to a clinically evident syndrome [82, 83].

### 13.7.2 Decreased CBF

As we have seen, microvascular compromise can result from inflammation. Studies [84, 85] with neuroimaging techniques have shown a decrease in CBF in delirious patients not only in sepsis but also in other clinical states. In particular, in a study with computed tomography (CT), researchers found a reduction in CBF of 43% in patients during delirium and even more in the frontal lobes [84]. Therefore, a reduction in CBF may be a common pathway of delirium in sepsis and other conditions. Too few studies have been published up to now to draw definitive conclusions. Further studies are needed to explore the role of reduced CBF in the development of delirium.

### 13.7.3 Neurotransmitter Imbalance

Clinical findings of the deliriogenic properties of some anti-cholinergic medications suggest that alterations in acetylcholine and the monoamines (dopamine, norepinephrine, and serotonin) levels within the central nervous system may predispose the development of delirium [74]. Many of the risk factors, such as anesthetics and opiates, can affect the release of acetylcholine and the availability of postsynaptic receptors. Moreover, some drugs routinely used during anesthesia as opiates or volatile anesthetics may affect acetylcholine release at neuronal synapses [86].

As we have already pointed out, inflammation itself may be responsible for an imbalance in production of neurotransmitters. In particular, acetylcholine deficit can be induced by ischemia or through a direct inhibitory effect of inflammatory mediators [87]. Nevertheless, trials conducted with cholinesterase inhibitors showed no effects in terms of prevention and treatment of delirium [88, 89]. These findings are consistent with a multifactorial hypothesis in the genesis of delirium.

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### 13.8 Approaches to Prevention and Treatment

In ICU, before initiating any treatment, physicians must address and rule out all the life-threatening complications of critical illness that may lead to delirium such as hypoxia, hypercapnia, hypoglycemia, shock, etc., identify possible discontinuation of patient's psychiatric medications, and check for exposure to deliriogenic drugs. Only at that point, both non-pharmacological and pharmacological treatments should be considered. Non-pharmacological multicomponent approaches are widely renowned as the most effective strategies for reducing frequency and duration of delirium [90]. In the non-ICU setting, risk factor modification has resulted in a 40% relative reduction in the development of delirium [91]. In particular, early mobilization, sensory reorientation, favoring natural sleep, earplugs, eye masks, noise control strategies, pharmacy medication review (i.e., reducing the exposure to "deliriogenic" drugs), music therapy, physical therapy, cognitively stimulating activities, family presence, bright light therapy, and education and orientation programs are proven to be effective strategies (some in the non-ICU and others in the ICU patients as well) [37, 50, 62, 91–93]. On the contrary, no convincing and reproducible evidence of effectiveness exists regarding the use of antipsychotics to prevent and treat delirium in ICU. In fact, some trials demonstrated no significant differences in rates of delirium between groups [94–96]. In some others, there was a reduction in the incidence of delirium but no effects in terms of clinical outcomes (complications, mortality, and hospital length of stay) or either they were not measured [97, 98]. A trial conducted with rivastigmine was halted because of an increase in mortality in the treated group [88]. Besides, the heterogeneity of the populations studied in the different trials makes it difficult to draw any conclusion. By the way, there is no evidence at the moment that treatment with haloperidol reduces the duration of delirium in adult ICU patients, whereas atypical antipsychotics (risperidone, olanzapine, quetiapine) may do. Moreover, antipsychotics are not recommended in patients at significant risk of torsade de pointes (i.e., patients with baseline or medication induced prolongation of QTc interval) [99]. Some encouraging results came from one recent double-blind randomized controlled trial in which post-cardiac surgery patients receiving dexmedetomidine (an  $\alpha_2$  agonist) for prevention purposes had a reduced incidence of delirium [100]. Regarding the treatment of established delirium, a study comparing dexmedetomidine with haloperidol in patients with hyperactive delirium, dexmedetomidine was associated with a shorter time to extubation and shorter ICU length of stay [101]. Therefore, currently

available guidelines suggest administering continuous IV infusions of dexmedetomidine for sedation to reduce the duration of delirium in adult ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal [99].

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## Conclusions

Delirium in the critically ill is a frequent and often under-recognized condition, burdened by an increased risk of prolonged mechanical ventilation, longer hospitalization, medium- and long-term cognitive impairment, and death. This is because delirium is far from being a temporary attenuation of brain function, usually followed by a full remission, but it is associated with the activation of complex neuronal pathophysiological pathways that may have not only acute but also long-term effects. Therefore, early recognition and treatment, as well as preventive measures, are of paramount importance. Clinical guidelines strongly support and recommend the use of specific diagnostic scales, which have to be applied routinely at the bedside. Guidelines also recommend non-pharmacological prevention and treatment strategies, whereas no sufficient level of evidence recommends the use of antipsychotics to prevent and treat delirium in the ICU.

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## 14.1 Assessment of Pain in Neonates, Infants, and Children

Discomfort, stress, or pain in pediatric intensive care unit (PICU) may be associated with routine patient care (e.g., physical examination and diaper changes), moderately invasive care measures (e.g., suctioning, phlebotomy, and peripheral intravenous [IV] line placement), or more invasive procedures (e.g., chest tube placement or central intravenous line placement). Care providers should prevent all infants from experiencing any form of pain. Detection and assessment of pain and its intensity is difficult in infants because of their inability to communicate with care providers. Along the chapter the standard nomenclature as defined by the neonatal pain control group of the Newborn Drug Development Initiative will be utilized [1].

Historically, pain prevention and control have been underutilized in neonates because of several misconceptions, such as:

- The pain pathways in neonates are unmyelinated or otherwise immature and cannot transmit painful stimuli to the brain.
- There is no alternative for verbal self-report, which remains the “gold standard” for conveying a subjective experience like pain.
- Pain perception is located only in the cortex, and thalamocortical connections must be fully developed in order to allow pain perception.
- The human infant does not have the psychological context in order to identify any painful experience until 2 years of age.
- Newborn infants are at greater risk for developing the adverse effects of analgesic or sedative agents, or these drugs have adverse long-term effects on brain development and behavior.

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There is no scientific evidence supporting these misconceptions. On the contrary, beginning in the 1980s, accumulating evidence demonstrated that both preterm and term infants experience pain and stress in response to noxious stimuli [2–4]. By the middle of the second trimester, the human fetus has a highly differentiated and functional sensory system [5–7]. This system appears to transmit different sensory modalities, like pain, touch, or vibration sense, which are mediated by very different pathways and loci of sensory processing in the mature adult nervous system. Numerous studies have documented neonatal responses to pain, which include autonomic (e.g., increases in heart rate, blood pressure), hormonal (e.g., cortisol and catecholamine responses), and behavioral changes (e.g., facial grimace) [2, 8–16].

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## 14.2 Types of Neonatal Pain

Pain in the neonate can be classified into three categories [17]:

- Acute or physiological pain—Occurs from skin-breaking procedures or tissue injury caused by diagnostic or therapeutic interventions. Infants admitted to the neonatal intensive care unit (NICU) repeatedly experience acute pain from an average of 12–16 invasive procedures each day [18, 19].
- Established pain—Occurs following surgery, localized inflammatory conditions (e.g., abscess or thrombophlebitis), or birth-related trauma.
- Prolonged or chronic pain—Results from severe diseases such as necrotizing enterocolitis (NEC) or meningitis.

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## 14.3 Neonatal Brain Response to Pain

Neuroimaging and neurophysiological studies have reported the following brain responses to painful stimuli in both preterm and term infants [20–22]. In preterm infants, near infrared spectroscopy (NIRS) has demonstrated increased cortical activation in the somatosensory areas of the brain in response to painful stimuli (e.g., heel stick or venipuncture) [20, 21]. Simultaneous imaging and physiologic testing using NIRS and electroencephalography also confirmed cortical activation with greater temporal and spatial resolution [22]. In term infants less than 7 days old, functional magnetic resonance imaging (fMRI) studies identified brain activation in 18 of the 20 brain regions typically activated in healthy adults following noxious stimulation [23]. There was no activation in the infant amygdala or orbitofrontal cortex. These results demonstrate that sensory and affective components of pain are active in infants and suggest that the infant pain experience closely resembles that of adults. Painful procedures are common in infants, especially in those in the PICU. Analgesic therapy is often not given, despite greater understanding that neonates experience pain [18, 19].

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## 14.4 Effects of Inadequately Treated Pain

Accumulating data suggest that untreated or inadequately treated neonatal pain may have long-term deleterious effects on pain response and neurodevelopmental outcome. Several studies have reported that exposure to repetitive pain in early life may lead to greater risk of developing increased pain sensitivity and/or chronic pain syndromes during their subsequent lifespan [24]. For example, infants of diabetic mothers, who were exposed to repeated heel sticks just after birth, exhibited more intense pain responses (facial grimacing and crying) during later venipuncture compared with normal infants. Infants exposed to gastric suctioning at birth evidenced threefold greater odds of developing irritable bowel syndrome during adolescence. These findings and other animal studies substantiate the theory that repeated exposure to neonatal pain leads to permanent changes in pain processing [24]. Interventions that reduce neonatal pain/stress also improve clinical outcomes. In postoperative infants, those who received greater amounts of anesthesia and analgesia compared with controls had reduced levels of norepinephrine, epinephrine, glucagon, aldosterone, and cortisol; decreased postoperative morbidity (e.g., sepsis, metabolic acidosis, disseminated intravascular coagulation); and a lower mortality rate [8].

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## 14.5 Neurodevelopmental Outcome

Neuroimaging, neuroendocrine, and neurobehavioral studies have also shown the neurodevelopmental impact of repetitive neonatal pain on long-term outcomes [25]. Frequency of exposure to neonatal pain-related stress has been correlated with subsequent impairments in cognitive development, altered neurocognitive processing, decreased cortical thickness, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Thus, we can conclude that it is essential to identify, assess, and manage neonatal pain effectively in order to minimize its impact on the intermediate- and long-term outcomes.

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## 14.6 Pain Assessment

Effective neonatal and infant pain assessment is an essential prerequisite for optimal pain management. Accurate neonatal pain assessment tools are required because of the inability of the infant to self-report. Neonatal pain assessment tools rely on surrogate measures of physiologic and behavioral responses to pain or noxious stimuli:

- Physiologic parameters—Changes in heart rate, respiratory rate, blood pressure, vagal tone, heart rate variability, breathing pattern, oxygen saturation, intracranial pressure, palmar sweating, skin color, or pupillary size.

- Behavioral responses—Crying patterns, acoustic features of infant crying, facial expressions, hand and body movements, muscle tone, sleep patterns, behavioral state changes, and consolability. In infants, total facial activity and cluster of specific facial findings (brow bulge, eye squeeze, nasolabial furrow, and open mouth) are associated with acute and postoperative pain [9, 13–16]. The scales most commonly used in this setting [26] are listed in Table 14.1.

Of note, a single assessment tool has not been adopted universally because each tool was developed and validated for selected populations and clinical settings. Research efforts to improve the objectivity and accuracy of assessment tools are

**Table 14.1** Commonly used measures of neonatal and infant pain

Measure and variables included	Age	Types of patient and pain evaluated	Score
PIPP (Premature Infant Pain Profile: heart rate, oxygen saturation, facial actions)	0–1 month	Sedated patient Procedural pain	Score $\geq 13$ : moderate or severe pain
NIPS (Neonatal Infant Pain Scale: facial expression, crying, breathing, movements, arousal)	0–1 m (until 40 <sup>th</sup> weeks of GA + 4 weeks)	Not sedated Procedural pain	Score $\geq 6$ : moderate or severe pain
CRIES (Cry, Requires oxygen, Increased vital signs, Expression, Sleeplessness)	0–6 mm (GA $\geq 32$ weeks)	Not intubated Postoperative pain	Score $\geq 6$ : moderate or severe pain
COMFORT scale (movement, calmness, facial tension, alertness, respiration and heart rate, muscle tone, blood pressure)	>1 m	Sedated, intubated, or not Postoperative pain, critical care. Recently validated for postoperative pain from 0- to 3-year-old infants	Score 6–10: excessively sedated patient Score 11–22: adequately sedated patient Score 23–30: not adequately sedated patient
FLACC (Face, Legs, Activity, Cry, Consolability)	1 m–<4 years	Not sedated	Score $\geq 4$ : moderate to severe pain
VAS (Visual Analog Scale)	$\geq 4$ years	Not sedated	Score $\geq 4$ : moderate to severe pain

At our institution, we assess pain at least every 4 h when vital signs are measured and after each painful or therapeutic intervention. In detail we use:

*The PIPP scale for the evaluation of procedural pain in sedated and intubated neonates*

*The NIPS for the assessment of procedural or acute pain in not sedated neonates*

*The CRIES for the assessment of postoperative pain in not intubated infants*

*The COMFORTneo scale for all types of pain in sedated or intubated infants aged more than 1 month*

*The FLACC scale for not sedated infants and children aged less than 4 years*

*The VAS scale in children aged more than 4 years*

ongoing. These include using neuroimaging (fMRI and NIRS) and neurophysiologic techniques (amplitude-integrated electroencephalography [aEEG], changes in skin conductance, and heart rate variability) during acute or prolonged pain [20, 21].

The following challenges limit the ability of available tools for accurate evaluation [26]:

- Interobserver variability and subjectivity—Many signs used in these assessment tools require the subjective evaluation by observers. As a result, there is significant interobserver variability in the evaluation of behavioral responses. In addition, many tools require the observation, mental calculations, and recording of three to ten parameters in real time by the bedside nurse. Often, the nurse performing the painful procedure is also tasked with observing the infant's pain responses at the same time.
- Since there is no “gold standard” established for pain in the neonate, the concurrent validity of many assessment tools has been questioned.
- Neuroimaging or neurophysiologic approaches used for research have not reached a level of sensitivity or specificity where they can be accepted as “the gold standard” for testing the accuracy of subjective assessment methods.
- Pain assessment tools generally do not take into account the type of the nociceptive stimulus or the body region where it occurs. For example, very limited data are available on visceral pain or bone pain in newborn infants.

Finally, most tools evaluate acute pain, and some evaluate postoperative pain, but do not assess persistent or prolonged pain. The definition of prolonged or chronic pain in newborns remains unclear. As a result, tools for the assessment of persistent or prolonged pain in neonates (due to major surgery, osteomyelitis, or necrotizing enterocolitis [NEC]) have not been developed or completely validated. During episodes of persistent pain, neonates may enter a passive state, with limited or no body movements, an expressionless face, reduced variability in heart rate and respiratory rate, and decreased oxygen consumption [24]. Thus, assessment tools based on these indicators will not adequately detect and assess the intensity of prolonged neonatal pain. The EDIN (Echelle de Douleur et d'Inconfort du Nouveau-né) and COMFORTneo scale were tools specifically developed for assessing prolonged neonatal pain [23]. Although they are used widely, these tools have not been extensively validated. Most assessment tools were developed for non-ventilated infants. However, several have been used in mechanically ventilated infants, including COMFORTneo scale [27].

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## 14.7 Prevention and Treatment of Pain in Neonates, Infants, and Children

Preemptive analgesia before and during elective painful procedures should be provided to all neonates. Analgesia often includes a combination of non-pharmacologic and pharmacologic techniques. In our institution, we use a combination of measures for frequently performed neonatal procedures in a stepwise manner with increasing



analgesia as the degree of anticipated procedural pain increases [28]. This approach follows the World Health Organization (WHO) analgesic workflow for pain management in adults and guidelines and the American Academy of Pediatrics national professional bodies [29].

- Step 1—Non-pharmacologic measures including breastfeeding, pacifier use, facilitated tucking or swaddling, skin-to-skin contact (kangaroo care), sensorial saturation, and the administration of oral sucrose. In many settings (e.g., heel stick), a combination of measures is used, such as oral sucrose and skin-to-skin contact.
- Step 2—Topical anesthetics (i.e., topical lidocaine, lidocaine-prilocaine cream, amethocaine gel, tetracaine gel).
- Step 3—Oral, intravenous (IV), or rectal administration of acetaminophen.
- Step 4—Slow IV infusion of opioids (e.g., fentanyl or morphine).
- Step 5—Subcutaneous infiltration of lidocaine or specific nerve blocks.
- Step 6—Deep sedation (e.g., combination of opioids, sedatives, and other drugs) or general anesthesia.

**Table 14.2** Management strategy for the most common neonatal and infants’ procedures

Non-pharmacologic measures (e.g., facilitated tucking or skin-to-skin contact) are used to improve analgesia for any painful procedure, when feasible
For neonates undergoing a <i>brief needlestick</i> (e.g., heel stick, venipuncture), oral <b>sucrose</b> is administered in combination with non-pharmacologic measures
For neonates undergoing a more prolonged or <i>painful skin-breaking procedure</i> (arterial puncture, arterial or venous line placement, or lumbar puncture), in addition to oral <b>sucrose</b> and non-pharmacologic measures, a topical anesthetic cream (e.g., eutectic mixture of local anesthetics [EMLA]) is used
For neonates who undergo <i>more invasive procedures, such as central line placement</i> , combinations of non-pharmacologic measures, local/topical anesthesia, and/or systemic analgesia are used to provide adequate analgesia
A combination of non-pharmacologic approaches, <b>acetaminophen</b> , and opioid therapy are used to provide <i>adequate postoperative analgesia</i>
<i>In mechanically ventilated neonates</i> , we do not routinely use continuous infusions of opioid therapy for analgesia
Newborns receiving <i>mechanical ventilation who have no other sources of pain</i> (e.g., <i>chest tubes, arterial or central venous lines</i> ) can be managed safely with intermittent doses of analgesic (e.g., IV <b>morphine</b> or <b>acetaminophen</b> ) or sedative agents (IV <b>lorazepam</b> ) given specifically for agitation or discomfort that are not controlled with non-pharmacologic approaches or <b>sucrose</b>
For <i>severe agitation in mechanically ventilated newborns</i> , low-dose continuous infusions of <b>dexmedetomidine</b> or <b>fentanyl</b> may be justified, with the goals being to limit opioid exposure, convert to oral agents, and prevent tolerance
Newborns with <i>chronic or persistent pain</i> (e.g., necrotizing enterocolitis [NEC], meningitis, and osteomyelitis) must receive adequate analgesia, usually with opioid infusions ( <b>morphine</b> or <b>fentanyl</b> ), regardless of whether they are mechanically ventilated or not. <b>Methadone</b> or <b>ketamine</b> can also be used to treat the hyperalgesia associated with persistent pain of this magnitude. The use of <b>gabapentin</b> or other chronic pain drugs may be considered after consultation with a neonatal pain service [30]

The application of these steps to specific invasive procedures at the bedside depends upon the clinician's choice and hospital-specific policies and procedures (Table 14.2). In most settings where there is a need to accelerate the steps of intervention, it is important to note that less invasive interventions are still provided. For example, the neonate should ideally receive oral sucrose (Step 1), topical anesthetics (Step 2), and subcutaneous administration of lidocaine (Step 5) when a central line is placed.

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## 14.8 Non-pharmacological Analgesia

The following non-pharmacologic approaches can effectively reduce pain and discomfort from routine care measures and minor procedures (e.g., heel stick) in both neonates and infants [31–33]:

- Breastfeeding (it may not be applicable to intubated or very preterm neonates)
- Non-nutritive sucking
- Swaddling or facilitated tucking (defined as gently maintaining the arms and legs in a flexed position)
- Skin-to-skin contact (e.g., kangaroo care)
- Sensorial saturation (use of touch, massage, voice, and smell)

Non-pharmacologic approaches are generally more effective when used in combination than when used alone. As discussed above, in our practice we use combinations of non-pharmacologic and pharmacologic measures depending upon the clinical setting. Combinations of non-pharmacologic measures (e.g., sucrose and skin-to-skin contact) have additive or synergistic effects. In some settings, these combinations may eliminate pharmacologic use or reduce drug dosage or the frequency of doses required and, consequently, the risk of pharmacologic side effects [32].

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## 14.9 Pharmacological Analgesia

Pharmacologic therapy for pain control in infants and children includes:

- Local analgesia including topical anesthetics and lidocaine

The following topical anesthetics are available:

Eutectic mixture of local anesthetic (EMLA) cream, a mixture of lidocaine-prilocaine (each 2.5%) in a cream base. Systemic reviews have shown that EMLA is efficacious and safe for procedural pain reduction in newborns [34].

Alternatively, 2% or 4% tetracaine cream can be used: it is a tetracaine gel that produces anesthesia within 30 min of its application with a duration of action of 4–6 h.

Finally, 4% or 5% liposomal lidocaine (it can be injected locally to reduce the pain associated with venous or arterial puncture, percutaneous venous or arterial catheter placement, LP). It is also used during surgical operations to reduce the postoperative hyperalgesia and need for postoperative analgesia.

- Systemic analgesia including opioid therapy

Systemic pharmacologic agents reducing pain and stress in PICU include non-opioid analgesics (e.g., acetaminophen and ketamine), nonsteroidal anti-inflammatory agents, and opioid analgesics (e.g., morphine, fentanyl, and methadone) [35].

### 14.9.1 Acetaminophen

Acetaminophen (paracetamol, N-acetyl-p-aminophenol) acts by inhibiting cyclooxygenase and consequently prostaglandin production in the central nervous system. It exerts a selective inhibition on cyclooxygenase pathway, and so it presents a mild anti-inflammatory but mainly analgesic (for treatment of mild to moderate pain) and antipyretic effect.

Analgesic effect of acetaminophen is related to (1) cyclooxygenase inhibition in peripheral nerve endings that stops the onset of algal stimulus, (2) reduction of neuronal interconnections with consequent interference in the spinal cord-cortex transmission of the nociceptive stimulus, and (3) activation of serotonergic descending pathways with modulation on primary nociceptive afferents.

Acetaminophen (paracetamol) has been used in the management of mild to moderate procedural and postoperative pain. However, acetaminophen alone is not effective enough to reduce acute pain [36]. Data suggest that acetaminophen may be useful in combination with opioids in order to reduce the overall amount of administered drugs [37]. In one trial, the use of IV acetaminophen reduced the cumulative morphine dose following major thoracic (noncardiac) or abdominal surgery: on average, the morphine dose was reduced by 66% in infants (49% reduction in newborns 0 to 10 days of age and 73% reduction in infants 11 to 365 days of age), with no differences in their pain scores or adverse effects [38].

#### 14.9.1.1 Pharmacokinetics and Pharmacodynamics

Acetaminophen has a neutral pKa (dissociation constant) and low plasma protein binding, so it easily crosses the blood-brain barrier and reaches the central nervous system where it exerts its anti-inflammatory action by inhibiting the pathway of cyclooxygenase. The peak of plasmatic concentration occurs 15 min after intravenous administration, about 40 min–1 h after oral administration, and 3–4 h after rectal administration. Acetaminophen half-life is about 1–4 h. Its metabolism occurs in the liver: acetaminophen enters in enterohepatic circulation, where most of the parent drug is removed by conjugation. A small fraction is oxidized by cytochrome P450 (mostly the isoforms CYP2E1, CYP1A2, and CYP3A4) to form the reactive metabolite (N-acetyl-p-benzoquinone imine, NAPQI). NAPQI is efficiently detoxified by

glutathione, determining the formation of conjugate 3-(glutathione-S-yl)acetaminophen, which is converted to acetaminophen mercapturate and excreted by the kidney [39]. Due to its high bioavailability, acetaminophen can be administered through various routes.

### 14.9.1.2 Formulation and Dosing

In infants, both rectal and IV formulations of acetaminophen are available.

In both preterm and term infants, the clearance of acetaminophen is slower than in older children, so oral dosing is required less frequently [40]. Single oral doses are 10–15 mg/kg given every 6–8 h and 20–25 mg/kg given rectally at the same time intervals. These doses and dosing intervals were primarily based upon antipyretic dose-response studies.

The following dosing schedule for infants with postmenstrual age (PMA) between 32 and 44 weeks has been proposed:

- Loading dose of 20 mg/kg
- Maintenance doses of 10 mg/kg starting 6 h after the initial dose and every 6 h thereafter

Recommended total daily doses are based on gestational and postnatal age [41]:

- 24–30 weeks gestation—20–30 mg/kg/day
- 31–36 weeks gestation—35–50 mg/kg/day
- 37–42 weeks gestation—50–60 mg/kg/day
- 1–3 months postnatal—60–75 mg/kg/day

In 2011, an intravenous formulation of acetaminophen was approved by the Food and Drug Administration in the United States. The recommended dosing is based on age and weight of the patient as follows:

- Children between 2 and 12 years of age
- Single dose: 15 mg/kg every 6 h
- Ongoing use: 12.5 mg/kg every 4 h (maximum daily dose, 75 mg/kg per day)
- Adolescent with a weight < 50 kg
- Single dose: 15 mg/kg every 6 h
- Ongoing use: 12.5 mg/kg every 4 h (maximum daily dose, 75 mg/kg per day)
- Adolescent with a weight ≥ 50 kg
- Single dose: 1000 mg every 6 h
- Ongoing use: 650 mg every 4 h (maximum daily dose, 4000 mg per day)

### 14.9.1.3 Side Effects

Adverse effects of acetaminophen occur rarely in infants, but caution should be used in infants with malnutrition and hypoalbuminemia [37]. In contrast to its use in older children and adults, acetaminophen rarely causes hepatic or renal toxicity in neonates. In addition, IV administration of acetaminophen does not increase the risk of hypothermia in neonates.

## 14.9.2 Nonsteroidal Anti-inflammatory Drugs

Although nonsteroidal anti-inflammatory drugs (NSAIDs) are used extensively in older children and adults, they are less commonly used in the neonatal period because of their well-known adverse effects in newborn infants. NSAIDs exert their anti-inflammatory and analgesic effect inhibiting prostaglandin synthesis through a nonselective inhibition of cyclooxygenase pathway.

In PICU NSAIDs are used both for their anti-inflammatory effect and for controlling pain as first-line analgesics. They have also clearly shown to enhance the analgesic effect of other drugs (like opioids or acetaminophen). In fact, some studies show that postoperative NSAIDs may have a sparing effect in the administration of other drugs [42]. Among NSAIDs, the drug most frequently used in PICU to control moderate pain is ketorolac. Another drug that is usually used to treat acute mild pain, which associates the analgesic and antipyretic effect, is ibuprofen, orally or intravenously administered at a dose of 10 mg/kg [43].

### 14.9.2.1 Pharmacokinetics and Pharmacodynamics

Ketorolac is bound to plasmatic proteins for 99%; it's metabolized in the liver via conjugation and it's renally excreted. Ketorolac onset is about 30 min and its half-life is 3–6 h. Recommended intravenous dose is 0.5 mg/kg every 8 h for a maximum length of treatment of 72 h in children <2 years of age and a maximum length of treatment of 5 days in older children [44].

### 14.9.2.2 Side Effects

The main side effects related to NSAID use are renal dysfunction, gastrointestinal effects, and bleeding due to clotting disorders. In clinical practice, often the risk of these side effects limits the use of NSAIDs after complex surgery. Nevertheless, some studies have shown that even after major surgical procedures the use of ketorolac does not increase the risk of bleeding and renal dysfunction [45–47].

### 14.9.2.3 Use in Newborn

Although some studies report data related to safe use of NSAIDs in neonates [48, 49], Aldrink et al. in 2011 demonstrated that patients under 21 days and corrected gestational age < 37 weeks have an increased risk of gastrointestinal bleeding in association with the administration of ketorolac. Particularly, gastrointestinal bleeding is more frequent in patients who do not receive enteral feeding but exclusively parenteral nutrition [50].

## 14.9.3 Opioid Therapy

Opioids are the most effective therapy for moderate to severe pain in patients of all ages. They provide both analgesia and sedation, have a wide therapeutic window, and also attenuate physiologic stress responses. Morphine and fentanyl are the most commonly used opioids in neonates, although more potent (e.g., sufentanil),

shorter-acting (e.g., alfentanil, remifentanil), or mixed opioids (e.g., tramadol) are being used with increasing frequency [35]. All opioids have activity at an opiate receptor, including agonists, antagonists, and mixed agonist-antagonists. Efficacy of opioid analgesics is primarily due to binding to the  $\mu$ -opioid receptor [35]. However, at least four discrete opiate receptors have been identified in the central nervous system (CNS), accounting for multiple potential side effects.

Risks versus benefits of opioid administration are assessed daily in critically ill patients, with vigilance for recognition of the development of these opioid-associated side effects [51]:

(1) Depressed consciousness and depression of respiratory drive. However, it is important to reduce total opioid dose in spontaneously breathing patients, particularly during weaning from mechanical ventilation. Patients most vulnerable to adverse consequences of respiratory depression include those with underlying chronic respiratory disease or renal and/or hepatic insufficiency that may alter opioid metabolism and elimination. The goal should be to use the minimally effective dose to achieve pain control. Treatment with naloxone is reserved for progressive obtundation suggestive of imminent respiratory failure. If spontaneous ventilations are still present, naloxone is administered in small, initial 0.04 mg bolus injections of dilute solution. Administration of naloxone may cause sudden reversal of pain control, with tachycardia, hypertension, and pulmonary edema.

(2) All opioids act directly on blood and tissue cells to release histamine, which may produce flushing, tachycardia, hypotension, pruritus, and bronchospasm. Histamine release is inversely correlated with analgesic potency and is greatest with large doses of meperidine or morphine, while fentanyl and remifentanil release little histamine.

(3) Nausea and vomiting may occur due to opioid-induced direct stimulation of the chemoreceptor trigger zone. Treatment of nausea and vomiting in critically ill patients is similar to treatment in postoperative patients, initially with IV bolus doses of ondansetron or dexamethasone.

(4) Gastrointestinal (GI) transit may slow with prolonged opioid administration due to binding to local opiate receptors in the gut, resulting in ileus and constipation. Strategies to minimize this side effect include multimodal analgesia, opioid reduction, and opioid rotation.

(5) Increased intracranial pressure (ICP)—Fentanyl and other opioids may rarely cause an increase in ICP. The mechanism and clinical significance of this effect in children are unknown [51].

#### 14.9.3.1 Morphine

Morphine is the most commonly used opioid for analgesia in neonates and children. It has been used as a continuous infusion in ventilated infants or infants following major surgery or intermittently to reduce the acute pain associated with invasive procedures. Whether it is an effective and safe neonatal analgesic in these clinical settings remains under active investigation. In ventilated term neonates, continuous morphine analgesia may not be associated with the same risk of adverse effects as those seen in preterm infants, but still may cause an increased duration of

**Table 14.3** Most commonly used opioids in PICU—dosing and warnings

Morphine	Bolus: 0,05–0,2 mg/kg (ev) Inf.: 0,01–0,02 mg/kg/h Until 0,4 mg/kg/h (ev)	Metabolite accumulation (M6-glucuronide) Slower tolerance Histamine release → hypotension
Fentanyl	Bolus: 1–3 mcg/kg (ev) Inf.: 1–5 mcg/kg/h Until 10 mcg/kg/h (ev)	Rapid tolerance and withdrawal syndrome
Remifentanyl	I.C.: 0,1–3 mcg/kg/min	Shorter half-life Rapid tolerance
Sufentanil	I.C.: 0,2–2 mcg/kg/h	Rapid onset (3–5 min) Hepatic metabolism Not recommended on high intracranial pressure, hypotension, cardiac failure, or vasoplegia
Methadone	Bolus: 0,1–0,2 mg/kg 0,05 mg/kg	Longer half-life

ventilation. A retrospective study of 62 ventilated term newborns found that postoperative morphine infusions prolonged the need for mechanical ventilation, but were not associated with apnea, hypotension, or other complications [52]. To date, there are no randomized controlled trials examining the effects of morphine analgesia in mechanically ventilated term neonates.

Onset of analgesia is 5–10 min, with peak effect occurring in 1–2 h. Recommended doses of morphine are presented in Table 14.3. Doses are titrated to the desired effect, with close monitoring for opioid-associated adverse effects.

Morphine has an elimination half-life of 3–5 h. After hepatic conjugation to glucuronide metabolites, renal elimination usually occurs within 24 h. Renal insufficiency permits accumulation of an active metabolite (morphine-6-glucuronide), which also has  $\mu$ -receptor-stimulating properties. Thus, dose adjustment is necessary to avoid oversedation and respiratory depression in patients with impaired renal function (creatinine clearance less than 30 ml/min) [53].

### 14.9.3.2 Fentanyl

In neonates, fentanyl is used because of its ability to provide rapid analgesia with minimal hemodynamic effects. However, there are no large trials of the use of fentanyl in neonates similar to those for morphine. Randomized controlled trials with smaller sample size have reported lower stress hormone levels (e.g., catecholamines and glucocorticoids), fewer episodes of hypoxia, and lower behavioral stress scores in ventilated infants treated with fentanyl compared with controls, but there were no differences in clinical outcomes between the fentanyl- and placebo-treated groups [54]. Fentanyl is a synthetic derivative of morphine. Compared with other opioids, fentanyl is virtually devoid of histamine-releasing properties. Thus, it is preferred in patients with hemodynamic instability or bronchospasm. Compared with morphine, it is approximately 100 times more potent and has faster onset of action due to



greater lipid solubility and improved penetration of the blood-brain barrier, although maximal analgesic and respiratory depressant effects of fentanyl may not be evident for several minutes.

Recommended doses of fentanyl are presented in Table 14.3. Typically, fentanyl is administered as a continuous IV infusion. Doses are titrated to the desired effect, with close monitoring for opioid-associated adverse effects [54]. Fentanyl is highly lipophilic, with rapid distribution to highly perfused tissues (e.g., brain, heart, kidney, and GI tract) and a slower redistribution to muscle and fat. Compared with morphine, fentanyl has a shorter half-life (2–3 h). It is metabolized in the liver to norfentanyl, an inactive metabolite that is then excreted in the urine. Renal insufficiency does not appear to affect its pharmacokinetics. However, stores in muscle and fat are mobilized after discontinuation of a fentanyl infusion and may result in prolonged sedation.

Fentanyl or its shorter-acting derivatives (e.g., alfentanil, remifentanil) are often used for achieving analgesia prior to tracheal intubation in newborns and infants.

Other indications include fentanyl analgesia for postoperative pain (particularly following cardiac surgery) or for patients with pulmonary hypertension (primary or secondary to meconium aspiration, diaphragmatic hernia, or congenital heart disease [CHD]). Despite the paucity of evidence for ventilated term or preterm neonates, or those exposed to postoperative or procedural pain, fentanyl analgesia is used frequently and widely in European NICUs.

Compared with morphine, fentanyl analgesia is associated with less sedative or hypotensive effects, reduced effects on gastrointestinal motility or urinary retention, but greater opioid tolerance and withdrawal [55]. In one randomized trial comparing infusions of fentanyl (1.5 mcg/kg/h) versus morphine (20 mcg/kg/h) in ventilated neonates, similar pain scores, catecholamine responses, and vital signs were reported in the two groups. There were no adverse respiratory effects or difficulties in weaning from ventilation in either group, but lower beta-endorphin levels and decreased incidence of gastrointestinal dysmotility occurred in the fentanyl group [55].

### 14.9.3.3 Remifentanil

Remifentanil is an ultrashort-acting fentanyl derivative with a rapid onset of action (<3 min), short duration of action (5–10 min after cessation of infusion), and analgesic potency approximately equal to fentanyl. Remifentanil may be considered in selected patients as the primary sedative-analgesic agent (e.g., when extubation is expected shortly after arrival to the ICU or frequent neurologic assessments are necessary) [56].

Recommended doses of remifentanil, administered as an infusion, are presented in Table 14.3.

Remifentanil is metabolized by nonspecific plasma esterases to inactive metabolites. Potential advantages include its rapid onset and offset and its lack of accumulation in patients with renal and/or hepatic dysfunction. Its use is limited due to concerns of tachyphylaxis, cost, and possible hyperalgesia after discontinuation.

#### **14.9.3.4 Methadone**

Methadone is a long-acting synthetic opioid with antagonist properties at the *N*-methyl-D-aspartate (NMDA) receptor. It has been used successfully to avoid withdrawal syndromes in critically ill patients and as an alternative to other opioids to alleviate high-dose opioid-induced hyperalgesia. Side effects of methadone include oversedation due to its long duration of action. Methadone prolongs the QTc interval, which may lead to torsades de pointes, a life-threatening cardiac arrhythmia. Electrocardiographic (ECG) documentation of the QTc interval is recommended before and at least every 8–12 h after initiation or increasing the dose of QTc-prolonging drugs.

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### **14.10 Sedative Agents for Pediatric Intensive Care**

A wide range of short-acting sedative-hypnotic and analgesic medications are available for pediatric intensive care setting [57]. Benzodiazepines, barbiturates, dexmedetomidine, and chloral hydrate provide sedation, anxiolysis, muscle relaxation, and amnesia. Sedative-hypnotic agents do not have analgesic properties and need to be combined with other analgesic agents to provide effective analgesia and sedation in critically ill patient.

#### **14.10.1 Sedative-Hypnotic Agents**

These drugs provide sedation, motion control, anxiolysis, and, to varying degrees, amnesia but, with the exception of dexmedetomidine, do not provide analgesia. The Food and Drug Administration is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in pediatric patients younger than 3 years may affect the development of children's brains. However, animal and recent human studies suggest that a single, relatively short exposure to general anesthetic and sedation drugs in infants or toddlers is unlikely to have negative effects on behavior or learning. Further research is still needed to fully characterize how early-life anesthetic exposure affects brain development.

##### **14.10.1.1 Propofol**

Propofol is a non-opioid, nonbarbiturate sedative hypnotic that has historically been extensively used by anesthesiologists and intensivists as an induction agent for general anesthesia and as a sedative in intensive care units [58].

#### **Dosing and Administration**

Recommended doses in children are the following:

Induction of general anesthesia: Children and adolescents (healthy) 3–16 years, ASA-PS 1 or 2: IV, 2.5–3.5 mg/kg over 20–30 s; use a lower dose for ASA-PS 3 or 4.

Maintenance of general anesthesia: Infants, children, and adolescents (healthy)  $\geq 2$  months to  $\leq 16$  years, ASA-PS 1 or 2: IV infusion, general range, 125–300 mcg/kg/min (7.5–18 mg/kg/h); initial dose immediately following induction, 200–300 mcg/kg/min; then decrease dose after 30 min if clinical signs of light anesthesia are absent; usual infusion rate after initial 30 min, 125–150 mcg/kg/min (7.5–9 mg/kg/h); infants and children  $\leq 5$  years may require higher infusion rates compared to older children.

Procedural sedation dose (limited data available) in infants, children, and adolescents: IV:

reported range for initial dose, 1–2 mg/kg; follow initial dose with 0.5 mg/kg every 3–5 min as needed until adequate level of sedation is achieved.

IV bolus followed by continuous infusion: Initial bolus, 1–2 mg/kg; continuous infusion, reported initial rate and titration are variable. In a large report of a pediatric sedation program in >4000 patients (age range, 1 month to 21 years), after an initial bolus of at least 2 mg/kg, an infusion was started at an initial rate of 9 mg/kg/h (150 mcg/kg/min) and titrated as required; supplemental doses of 1–2 mg/kg were used as needed; however, hypotension occurred in up to 42.5% of patients undergoing MRI and 23.2% of patients undergoing other procedures.

Hypovolemic children or those affected by cardiac disease should receive intravenous fluids to correct volume status prior to propofol sedation. For children with reduced cardiac output, attempts should be made to improve cardiac performance prior to sedation and dosing should be minimized.

Prolonged propofol infusions in critically ill patients have been associated with the propofol infusion syndrome, an acute refractory bradycardia that progresses to asystole in combination with metabolic acidosis, rhabdomyolysis, hyperlipidemia, and/or fatty liver.

Advantages: Potent sedative-hypnotic associated with an immediate onset and rapid awakening upon discontinuation when administered for short-term use. Metabolism is reportedly unaltered in hepatic or renal impairment and subject to few significant drug interactions. Infusion is readily titratable to desired depth of sedation, minimizing risk of oversedation. Propofol effectively decreases intracranial pressure, lowers cerebral metabolism, controls intractable seizures, and may reduce shivering in the rewarming phase of induced hypothermia following resuscitation from cardiac arrest.

Disadvantages: Adverse effects include hypotension, bradycardia, respiratory depression, decreased myocardial contractility, elevated triglycerides, and peripheral injection site pain. Specific product presentations may include potential allergens (egg, soy, peanut, others). However, observational evidence suggests that propofol may be used safely in patients with egg, soy, and peanut allergies. Thus, we do not view the history of allergy to these foods as a contraindication to the use of propofol. It has no analgesic effect.

Role: A good choice in conjunction with appropriate analgesia for short-term sedation of patients in whom rapid awakening is advantageous. Also a good choice to decrease elevated intracranial pressure or for short-term sedation in patient that is likely to be ready soon for ventilator weaning trials [59].

### 14.10.1.2 Midazolam

Midazolam is water soluble and can be given by parenteral (intravenous or intramuscular), rectal (PR), intranasal (IN), sublingual (SL), or oral (PO) routes. Doses, onset of action, and duration of effect will vary depending upon patient age and the route of administration. This agent has the most rapid onset of action and shortest recovery time [60].

Dosage must be individualized and based on patient's age, underlying diseases, concurrent medications, and desired effect; decrease dose (by ~30%) if opioids or other CNS depressants are administered concomitantly; use multiple small doses and titrate to desired sedative effect; allow 3–5 min between doses to decrease the chance of oversedation.

Sedation, anxiolysis, and amnesia prior to procedure or before induction of anesthesia:

- IM: Infants, children, and adolescents: Usual, 0.1–0.15 mg/kg 30–60 min before surgery or procedure; range, 0.05–0.15 mg/kg; doses up to 0.5 mg/kg have been used in more anxious patients; maximum total dose, 10 mg.
- IV: Infants 1–5 months: Limited data available in nonintubated infants; infants <6 months are at higher risk for airway obstruction and hypoventilation; titrate dose with small increments to desired clinical effect. Infants 6 months to children 5 years: initial, 0.05–0.1 mg/kg; titrate dose carefully; total dose of 0.6 mg/kg may be required; usual total dose maximum, 6 mg. Children 6–12 years: initial, 0.025–0.05 mg/kg; titrate dose carefully; total doses of 0.4 mg/kg may be required; usual total dose maximum, 10 mg. Children 12–16 years: dose as adults; usual total dose maximum, 10 mg.
- Intranasal (some investigators suggest premedication with intranasal lidocaine to decrease irritation and subsequent agitation): Infants ≥6 months, children, and adolescents, 0.2–0.3 mg/kg (maximum single dose, 10 mg).
- Oral: Infants >6 months, children, and adolescents ≤16 years: Single dose, 0.25–0.5 mg/kg once, depending on the patient status and desired effect; usual, 0.5 mg/kg; maximum dose, 20 mg; use lower initial doses (0.25 mg/kg) in patients with cardiac or respiratory compromise, concomitant CNS depressant, or high-risk surgical patients.
- Rectal: Infants >6 months and children: Usual, 0.25–0.5 mg/kg once.
- Sedation, mechanically ventilated patient: Infants, children, and adolescents: IV, loading dose, 0.05–0.2 mg/kg given slow IV over 2–3 min; then follow with initial continuous IV infusion, 0.06–0.12 mg/kg/h (1–2 mcg/kg/min); titrate to the desired effect; range, 0.024–0.36 mg/kg/h (0.4–6 mcg/kg/min).

Advantages: Midazolam has strong amnestic properties and is an effective anxiolytic in most children, with an immediate onset of action and a short duration of effect when administered short term (<48 h). It is the only IV benzodiazepine that is not delivered in propylene glycol. The many potential routes of administration permit its use also in children without vascular access. When used as the sole agent for sedation with proper dosing, respiratory depression is rare. Flumazenil is an

effective reversal agent for the few patients who develop significant respiratory depression or apnea after sedation with midazolam. Flumazenil should not be used in patients with seizure disorders or those who receive benzodiazepines on a chronic basis because of the risk of precipitating seizures or withdrawal symptoms, respectively.

**Disadvantages:** Hepatically metabolized by CYP3A4 to active metabolites that may accumulate and cause prolonged sedation if delivered long term. Half-life may be prolonged in critically ill patients with hepatic or renal impairment. Risk of delirium. Also, it interacts with drugs used in the ICU (e.g., some antiretrovirals, azole antifungals) that alter CYP metabolism such that excess sedation can occur with concomitant use of midazolam and drugs metabolized by CYP3A4.

Accumulating data in newborn animal models suggests that midazolam induces apoptosis and/or necrosis of neurons and other brain cells, independent of the benzodiazepine receptor, in the developing brain. These data add to our concerns regarding the long-term effects of using midazolam for sedation in term and preterm newborns.

It can cause respiratory depression and apnea, especially when combined with opioid medications such as opioids. Paradoxical reactions, including inconsolable crying, hyperactivity, and aggressive behavior, may occur in approximately 1–3% of patients when midazolam is used as a single agent.

**Contraindications and precautions:** It has mild negative inotropic effects and should be used with caution in children with underlying myocardial depression [60, 61].

**Role:** A good choice for short-term anxiolysis and treatment of acute agitation. Dose adjustment and gradual titration are needed for patients with renal and/or hepatic impairment.

### 14.10.1.3 Chloral Hydrate

Chloral hydrate was once the preferred sedative agent for diagnostic imaging in infants and children younger than 3 years of age and is efficacious for that purpose. However, small trials and observational studies indicate that chloral hydrate is inferior to other sedation options because of its delayed onset of action, prolonged effect, and high frequency of adverse effects. Given the availability of better alternatives, and possible drug toxicity, the use of chloral hydrate is no longer recommended.

### 14.10.1.4 Lorazepam

**Dosing and administration:** 0.02–0.06 mg/kg every 2–6 h intermittent (1–4 mg).

There are limited data in children and infants.

**Advantages:** Sedative, amnestic, potent anxiolysis with anticonvulsant properties. Hepatically metabolized by glucuronidation to inactive metabolites. Relatively low risk of drug interactions and safety in mild to moderate hepatic and renal impairment.

**Disadvantages:** Relatively slow onset. Risk of oversedation when titrating due to delayed response and accumulation in peripheral tissues. Risk of delirium. IV

incompatibilities and risk of line precipitate. Propylene glycol solvent may accumulate with prolonged use or high dosing causing metabolic acidosis and end-organ dysfunction. Long half-life, with significant risk of accumulation in the elderly or in patients with significant renal or hepatic impairment [62].

Role: A good choice for sedation and anxiolysis, including those who may require long-term ongoing sedation. Although intermittent bolus dosing may be preferred, a continuous infusion may be initiated for patients requiring frequently repeated higher dosing. It is used in withdrawal syndrome.

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## 14.11 Adjunctive Sedative

With regard to analgesia in children, we know that the central nervous system of fetus is anatomically and functionally able of perceiving a painful stimulus as early as 23 weeks of gestational age and that children up to 18 months of age have an immaturity of the inhibitory descending pathways, which determines reduced activation of pain modulation. Furthermore, in newborn age there is an overexpression of neurotransmitters that mediate nociception leading to an increased excitability of the transmission pathway located in the dorsal horn. The multiple mechanisms of action that lead to the development of the painful stimulus make it particularly useful to use several drugs to modulate pain perception. In critically ill pediatric patients admitted to the PICU, sedation may have multiple aims: the need to manage anxiety and fear, to tolerate minimally invasive procedures, to obtain adequate adaptation to mechanical ventilation, and to control pain. This involves the need for multiple components in the treatment: sedation (light or deep sedation depending on the patient's status), amnesia, analgesia, eventually neuromuscular block, and minimal hemodynamic impact. Since there is no single drug that includes all of these components, it is inevitable the use of multiple drugs that act at several levels.

For this purpose, adjuvant drugs are particularly useful. They are hypnotic and analgesic drugs that can be used in combination with drugs commonly used in the ICU (like propofol and benzodiazepines to obtain sedation, opioid and non-opioid analgesics to control pain) who act on different receptor sites enhancing the sedative and analgesic effects of conventional drugs.

It is very important to administer the correct dose of sedative and analgesic medications: an inadequate dose may cause discomfort, while an excessive one can result in occurrence of side effects, tolerance, and onset of withdrawal symptoms.

### 14.11.1 Alpha2 Receptor Agonists

Dexmedetomidine and clonidine are the drugs belonging to the class of alpha agonists most frequently used in clinical practice as first-line or adjunctive sedatives.

### 14.11.1.1 Dexmedetomidine

Dexmedetomidine, an isomer of medetomidine, is a selective agonist of  $\alpha_2$  receptors and used as a hypnotic and anxiolytic-sedative. Its action mechanism at the cellular level is based on the inhibition of adenylyl cyclases and the release of intracellular cAMP, resulting in reduced levels of calcium entering the nerve endings. Specifically, the sedative-anxiolytic effect is achievable by the activation of  $\alpha_2$ -adrenergic receptors, which are localized in pre- and postsynaptic endings of the locus coeruleus [63]. The mild analgesic effect, meanwhile, is due to stimulation of the  $\alpha_2$ -adrenergic receptors, which are localized at the level of the posterior horn of the spinal cord [64]. Dexmedetomidine continuous infusion, in combination with opioids and benzodiazepines, has been shown to provide an adequate level of sedation in children and to decrease the amount of overall administered sedatives (sparing effect) [65, 66]. As such, dexmedetomidine allows for the optimal sedation of patients and may contribute to a lower incidence of some of the side effects of opioids (respiratory depression, constipation, urinary retention) and benzodiazepines (dysphoria, confusion). Furthermore, its short half-life and ease of management guarantee an adequate level of sedation (light sedation) without respiratory depression and adequate anxiolysis associated with a good capacity of interaction with the surrounding environment.

### Clinical Application

In pediatric setting, dexmedetomidine use is now widespread in intensive care (where it is used in noninvasive ventilation [67, 68], in patients who need prolonged mechanical ventilation and prolonged infusion of sedative drugs), in catheterization lab [69], for intraoperative sedation in several branches of pediatric surgery, and in non-operating room anesthesia [70, 71]. An interesting field of application is the use of dexmedetomidine in PICU to counter the onset of delirium after prolonged administration of sedative or symptoms due to withdrawal [72, 73].

### Pharmacokinetics and Pharmacodynamics

The pharmacokinetic and pharmacodynamic characteristics of dexmedetomidine make it a useful drug for several administration routes: intravenous, intramuscular, orally, and intranasally using in premedication. The relatively short distribution half-life of about 6 min of dexmedetomidine results in rapid onset of sedation, and an elimination half-life of approximately 2 h facilitates clearance of the drug.

Dexmedetomidine is rapidly distributed and extensively metabolized in the liver and excreted in urine and feces. Dexmedetomidine undergoes almost 100% biotransformation, with very little excreted unchanged (<1%). It undergoes conjugation, N-methylation, hydroxylation, glucuronidation, as well as CYP450 metabolism. Ninety-five percent of metabolites is excreted through the kidney, and they have no significant pharmacological activity. The metabolism of the drug presents significant increase of half-life time ( $t_{1/2}$ ) in hepatic failure (7.5 h), while there is no significant effect of renal impairment.



#### Administration route and doses:

- Intranasal and oral (0.5–2 mcg/kg), mainly used for surgical premedication
- Intramuscular (2 mcg/kg)
- Intravenous: 0.2 mcg/kg/h to 1.4 mcg/kg/h in continuous infusion, also with loading dose of 1–2 mcg/kg administered in 10 min

#### Hemodynamic Effects

The loading dose should be administered with caution in patients with hemodynamic instability because it can lead to side effects. Most frequent side effects associated with dexmedetomidine use are hypotension and bradycardia [74, 75]. Consequently, the main contraindications in the use of the drug are hemodynamic instability and atrio-ventricular block. The hemodynamic effects are dose dependent and related to drug serum concentrations [76]. Usually the hemodynamic effects that are associated with the infusion of dexmedetomidine are easily managed without the need for suspension of the drug. Immediate action to treat bradycardia associated with  $\alpha_2$ -adrenergic agonists in children is required only if concomitant vital signs are abnormal, if bradycardia is caused by a serious primary bradyarrhythmia, or both. The occurrence of hypotension can be attenuated reducing infusion rate by 0.2 mcg/kg/min and administering fluids. If hypotension is marked, consider adding amine or discontinuation of therapy. If bradycardia is associated with hemodynamic instability, reduce by 0.2 mcg/kg/h the infusion rate and administer IV atropine 0.02 mg/kg. If bradycardia persists with hemodynamic instability at doses below 0.4 mcg/kg/h, stop the infusion for about 20 min and evaluate the association with infusion of amines, or stop dexmedetomidine infusion and evaluate sedation with another drug. Avoid or carefully consider dexmedetomidine administration in children receiving digoxin,  $\beta$ -adrenergic blockers, calcium channel blockers, or other agents that predispose to bradycardia or hypotension. The concomitant administration of dexmedetomidine with medications that have negative chronotropic effects (propofol, pyridostigmine, succinylcholine, and remifentanyl) may potentiate vagotonic or negative chronotropic.

#### Use in Newborn

Several studies [77, 78] demonstrated that neonates require smaller dose (30–40% less) than infants to obtain similar plasma concentrations at steady state. The greatest reduction is required in the first 2 weeks of life. The clearance of the drug in fact increases with age in the first month of life, and the time to steady state is increased in newborns probably due to the fact that liver enzymes involved in the metabolism of dexmedetomidine mature in the first month of life.

##### 14.11.1.2 Clonidine

Clonidine is an agonist of the alpha receptors less selective with respect to dexmedetomidine, as it binds both the  $\alpha_1$  and  $\alpha_2$  receptors with a predominant action on  $\alpha_2$ . By activation of central and peripheral  $\alpha_2$  receptors, clonidine leads to reduced norepinephrine release and sympathetic nervous activity with analgesic and sedative effect.

## Clinical Applications

In clinical practice, clonidine is used in pediatric anesthesia and intensive care medicine as a sedative agent that can be used in monotherapy to achieve sedative effect without respiratory depression [79], for surgical premedication [80], to facilitate weaning from other sedative agents and reduce the onset of withdrawal symptoms [81], and to spare anesthetics and postoperative analgesics [82].

## Pharmacokinetics and Pharmacodynamics

Clonidine is metabolized to 50% in the liver mainly by CYP2D6 and 50% is excreted in the urine.

Administration route and doses:

- Oral: it's used both for surgical premedication and in PICU. The oral bioavailability is about 55% [83] and recommended dose is 3–5 mcg/kg.
- Intravenous: 1–3 mcg/kg/h in continuous infusion, with possible loading dose of 0.5–1 mcg/kg.

## Hemodynamic Effects

As dexmedetomidine, the most easily observed hemodynamic effects following the use of clonidine are hypotension and bradycardia. They are dose-related effects that occur more frequently with intravenous administration, especially if preceded by loading dose. Several studies [84, 85] demonstrate that continuous infusion of clonidine does not cause cardiovascular effect which involves the reduction of the dose or discontinuation of treatment. In fact the drug is well tolerated in the categories of most unstable patients (i.e., patients undergoing cardiac surgery) [86].

## Use in Newborn

The immature elimination pathways (immaturity of hepatic metabolism and renal drug excretion capacity) in neonates may lead to reduced clearance (approximately one-third that described in adults). The optimal dose in this particular population is a function of clearance and should be reduced in neonates with respect to older children. Some studies demonstrated that the clearance of clonidine increases with postnatal age [87–89]. Since the hemodynamic effects of clonidine are dose dependent, neonates are the patient population most subject to onset of side effects.

### 14.11.2 Ketamine

Ketamine is a noncompetitive antagonist to the phencyclidine site of NMDA receptor for glutamate. Blocking glutamate effects on the cortical and limbic system, it causes a sedative, analgesic, and antegrade amnestic effect.

#### 14.11.2.1 Clinical Applications

In pediatric setting ketamine is used to obtain moderate sedation in PICU and during mini-invasive procedures. Moderate sedation is a drug-induced depression of

consciousness during which a patient is able to respond to verbal commands and to interact with the surrounding environment, depending on the patient's age. With moderate sedation, the patient maintains an adequate and spontaneous ventilation [90, 91]. Due to its ability to maintain the airway reflex and its bronchodilatory properties, ketamine is the first-line sedative agent in patients with status asthmaticus or bronchospasm who also require sedation [92]. It provides bronchodilation by increasing catecholamine transmission and stimulation of  $\beta_2$ -adrenergic receptors.

In children affected by cardiac heart disease, often ketamine is used in PCICU and in catheterization lab to maintain the airway reflex and sympathoadrenal hemodynamic stability [93].

#### **14.11.2.2 Pharmacokinetics and Pharmacodynamics**

Ketamine is a highly lipid-soluble drug with large volume of distribution (1.5–3.7 L/kg) and rapid clearance (0.7–2 L/h/kg). Its high solubility enables it to cross the blood-brain barrier rapidly. Onset of anesthesia is within 30 s. The context-sensitive half time of the drug is short (40 min after infusion discontinuation). Ketamine is eliminated by hepatic metabolism through N-demethylation to norketamine via CYP3A4 enzyme systems [93]. Norketamine is an active metabolite, which has lower power compared to ketamine (from 1/3 to 1/5 of the power of the original molecule). This metabolite is hydroxylated, conjugated, and finally excreted through the kidneys. The high ketamine clearance rate suggests that its elimination is susceptible to factors affecting hepatic blood flow.

#### **14.11.2.3 Administration Route and Doses**

- Intravenous: loading dose of 0.5–2 mg/kg followed by continuous infusion starting with 0.6 mg/kg/h, titrating up to a maximum dose of 3 mg/kg/h to achieve a targeted sedation or improvement in bronchospasm
- Intramuscular: 3–5 mg/kg
- Oral: 3–5 mg/kg
- Intranasal: 1–2 mg/kg

#### **14.11.2.4 Side Effects**

Possible side effects associated with the use of ketamine are:

- Increase of secretions, caused by activation of central cholinergic receptors
- Tachycardia and hypertension that are dose-dependent effects of ketamine associated with the release of endogenous catecholamines, often resulting in increased systemic vascular resistance
- Emergence reactions that are psychic effects occurring in approximately 12% of patients (i.e., delirium and hallucinations) [94]

In selected patients, ketamine may be associated with hypotension. This event occurs mainly in patients with sepsis, decreased myocardial contractility, hypovolemia, or cirrhosis, because its use is associated with the release of catecholamine

stores. These patients can be affected by depletion of endogenous catecholamines, and it results in direct negative inotropic properties [95].

### 14.11.2.5 Use in Newborn

CYP3A4 enzymes reach maturity within the first year of life, and ketamine plasma concentrations following administration of the same dose change with body weight (or age) [96]. Some studies demonstrate the need of higher infusion rates per kg to produce steady-state concentrations in younger (smaller size) children compared to older (larger size) children [97]. Literature regarding neonates is scant: recommended dosing, as established in a subset of NICU neonates, is 0.5–2 mg/kg in loading dose and 0.5–1 mg/kg/h in continuous infusion [30].

### 14.11.3 Neuromuscular Blockers

Neuromuscular blockers act on the nicotinic cholinergic receptors at the myoneural junction. The link with nicotinic postsynaptic receptor for acetylcholine nicotinic determines depolarization of the end plate with the consequent and progressive depolarization of the striated muscle fiber activating voltage-dependent sodium channels. This determines the mobilization of  $\text{Ca}^{++}$  from the tubules T and from the sarcoplasmic reticulum and consequent contraction for binding of calcium with the muscle contractile proteins (actin and myosin).

There are two different classes of neuromuscular blocker agents:

- Depolarizing (nicotinic receptor agonist)
- Non-depolarizing (nicotinic receptor antagonist)

Depolarizing agents (i.e., succinylcholine) bind acetylcholine receptor located on the myoneural junction, but their metabolism is slower than acetylcholine, and it determines a prolonged depolarization of motor end plate.

The non-depolarizing agents (pancuronium, vecuronium, rocuronium, atracurium, and cisatracurium) prevent the depolarization of the end plate preventing endogenous acetylcholine binding to receptors located on the plate (antagonist effect). Neuromuscular blockers are also distinguished by their molecular structure into two classes: aminosteroids (pancuronium, vecuronium, rocuronium) and benzylisoquinolines (atracurium and cisatracurium).

#### 14.11.3.1 Clinical Application

The use of neuromuscular blocking agents in PICU is necessary in some clinical conditions, i.e., to facilitate endotracheal intubation or difficult ventilation; to prevent patient-ventilator asynchrony; to decrease energy consumption in children affected by low cardiac output; to ensure the immobility during the execution of invasive procedures, during extracorporeal membrane oxygenation (ECMO), or in case of delayed sternal closure; or to allow wound healing. However, their use is associated with a high percentage of cases with the onset of critical illness

neuropathy or myopathy (1.7% as it was reported in a study conducted on a population of critically ill pediatric patients) [98]. In 2007 the United Kingdom Paediatric Intensive Care Society Sedation, Analgesia and Neuromuscular Blockade Working Group summarized the recommendations for the use of neuromuscular blocking agents in PICU as follows [99]:

1. The use of neuromuscular blocking agents must be associated with an adequate level of analgesia and sedation.
2. The need for neuromuscular blocking agents should be regularly reviewed, and they should be discontinued as soon as possible.
3. If patient's clinical conditions permit, continuous infusions of neuromuscular blocking agents should be discontinued at least once every 24 h until spontaneous movement returns and the levels of analgesia and sedation can be assessed.
4. Atracurium and vecuronium are the recommended agents for continuous infusions. If it's necessary, intermittent doses of pancuronium may be considered.
5. When continuous infusions are employed, the degree of neuromuscular blockade should be assessed at least once every 24 h with train-of-four monitoring titrating the dose to provide the optimum level of neuromuscular blockade.

#### **14.11.3.2 Pharmacokinetics and Pharmacodynamics**

Among neuromuscular blocking agents, succinylcholine has the shortest duration of action (4–6 min) and a rapid onset (<1 min).

Among non-depolarizing agents, rocuronium has faster onset (<1 min) and a maximum duration of action about 40 min; vecuronium, pancuronium, and cisatracurium have onset between 2 and 3 min; differently from pancuronium (that has maximum duration of action about 100 min, the longest duration among neuromuscular blockers), vecuronium, atracurium, and cisatracurium present a duration of action about 40 min.

Because of their different pharmacological structures with respect to the other neuromuscular blocking, atracurium and cisatracurium have no hepatic or renal metabolism (therefore it's not necessary to have a dosage adjustment according to renal or hepatic function of the patient), but they are metabolized by plasma cholinesterase (Hofmann degradation). This makes these drugs safe and useful as a continuous infusion. The most widespread use of cisatracurium with respect to atracurium is due to the fact that cisatracurium is four times more powerful than atracurium and presents a minor hemodynamic impact in terms of tachycardia and hypotension [42].

Recommended doses in children:

Vecuronium 0,1 mg/kg

Rocuronium 0,6–1 mg/kg

Pancuronium 0,1–0,15 mg/kg

Cisatracurium 0,1–0,15 mg/kg in bolus; 0,02–0,03 mg/kg/h in continuous infusion

Succinylcholine 1–2 mg/kg

### 14.11.3.3 Side Effects

Since neuromuscular blocking exercise their mechanism of action by modulating the action potential of nerve cells and the release of calcium into muscle cells, it is important to monitor electrolyte abnormalities: hyponatremia, hypokalemia, and hypocalcemia can potentiate the neuromuscular blockade, while hypomagnesemia may reduce it [100]. Side effects associated with the administration of neuromuscular blockers in bolus are mainly cardiovascular effects relating to steroid drugs. In particular, the administration of rocuronium can be associated with the onset of tachycardia, while vecuronium can cause tachycardia and hypertension. Among benzylisoquinoline drugs, atracurium may cause tachycardia and hypotension; on the contrary, cisatracurium has no side effect on the cardiovascular system. The main side effect associated with prolonged administration of neuromuscular blockers is critical illness myopathy.

The administration of most neuromuscular blockers, moreover, may be associated with the release of histamine and IgE-mediated allergic reactions, due mainly to the presence in their molecular structure of quaternary ammonium groups.

To reverse neuromuscular block, there are two types of drugs, neostigmine and sugammadex, more recently introduced in clinical practice. Sugammadex is a  $\gamma$ -cyclodextrin whose cyclic molecular structure comprises a cavity that is externally hydrophilic and internally hydrophobic. Sugammadex bind vecuronium and rocuronium in 1:1 ratio, reducing their free concentration and freeing the nicotinic receptors of the myoneural junction. Neostigmine is an anticholinesterase drug with nonselective reversible effect. Its mechanism of action involves the inhibition of cholinesterase (enzyme of acetylcholine degradation) in the synaptic space and the consequent increase of acetylcholine concentration. Acetylcholine binds nicotinic receptors with a competitive mechanism displacing non-depolarizing neuromuscular blockers.

### 14.11.3.4 Use in Newborn

Some studies demonstrated that neonates are more sensitive to the administration of neuromuscular blocking agents and require smaller doses of these drugs. They can have, at the same dosage, prolonged neuromuscular blockade compared to older children [101].

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## 14.12 Tolerance and Withdrawal Syndrome

Tolerance is a decrease in a drug's effect over time or the requirement of dose escalations to achieve the same level of sedation or analgesia. Tolerance is related to changes at or distal to the receptor, generally at the cellular level. Tolerance can be divided into subcategories: (1) innate tolerance, a genetically predetermined lack of sensitivity to a drug; (2) pharmacokinetic or dispositional tolerance, changes in a drug's effect because of alterations in its distribution or metabolism; (3) learned tolerance, a reduction in a drug's effect related to learned or compensatory

**Table 14.4** Sophia Benzodiazepine and Opioid Withdrawal Checklist (SBOWC)

1. Central nervous system irritability
• Agitation
• Anxiety
• Increased muscle tension and motor disturbance
• Slight muscle jerks
• Uncoordinated, robust movements
• Tremors: spontaneous, in response to stimuli
• Inconsolable crying
• High-pitched crying
• Grimacing
• Sleep pattern: sleeps <1 h, sleeps >1 and <3 h
• Seizures
• Pupil dilatation
• Hallucinations
2. Gastrointestinal dysfunction
• Vomiting
• Diarrhea
• Increased gastric residuals after feeding
• Poor feeding
3. Autonomic dysfunction
• Tachycardia
• Tachypnea
• Hypertension
• Fever
• Sweating
• Sneezing
• Yawning
• Mottling

Items were to be scored “yes” if the symptom had been present during the past 4 h. For the purpose of analysis, items assigned yes have to be recorded in the numeric value “1,” all other items as “0.” The sum score for each assessment was computed by summing the numeric values. The SBOWC sum score thus can range from 0 to 24 (no symptoms vs. all symptoms of withdrawal)

mechanisms (learning to walk a straight line while intoxicated by repeated practice); and (4) pharmacodynamic tolerance [102]. With pharmacodynamic tolerance, although the plasma concentration of the drug remains constant, there is a decreased drug effect. Pharmacodynamic tolerance results primarily from two mechanisms: (1) the receptor desensitization and (2) the upregulation of the cAMP pathway.

Withdrawal refers to the clinical signs and symptoms that occur when a sedative or analgesic agent is abruptly discontinued or pharmacologically reversed in a tolerant patient. The symptomatology of withdrawal varies significantly, being affected by several factors including the agent that has been administered and patient factors such as age, cognitive state, associated medical conditions, and comorbid states.

Tolerance and withdrawal are strictly linked and, in the PICU, essentially refer to patients with prolonged (>48–72 h) sedation and with an overall elevated cumulative amount of benzodiazepines (i.e., midazolam in the range of 70 mg/kg) and/or opioids [102].



The prevention of tolerance and withdrawal starts with the identification of patients who are likely to be physically tolerant followed by slowly weaning the sedative and analgesic agents in these patients. Even with shorter durations of administration (3–4 days), withdrawal scales should still be applied to all PICU patients following the discontinuation of sedative and analgesic medications as withdrawal can still occur with shorter durations of therapy. A checklist, named Sophia Benzodiazepine and Opioid Withdrawal Checklist (SBOWC), has recently been compiled [103]. It contains all symptoms of benzodiazepine and opioid withdrawal described in the literature specific to critically ill children. It is composed of 24 items (Table 14.4). Ista and coworkers were able to show that this scale was reliable and reproducible, and they were able to show that the frequency of withdrawal symptoms can be present in up to 100% of patients at risk. When a more prolonged course of opioid or sedative agent therapy will be necessary, switching to the oral administration of long-acting agents such as methadone or lorazepam should be considered. This practice may allow for earlier removal of venous access and hospital discharge. To date, the majority of experience from the literature resides in the transition from intravenous opioids generally fentanyl to the oral agent, methadone. Regardless of the agent or agents responsible for withdrawal, the role of dexmedetomidine in treating such problems is supported by animal studies [104], case reports in adults and children [105], and one retrospective case series in infants [106]. The latter is a retrospective analysis on seven infants ranging in age from 3 to 24 months that outlines the use of dexmedetomidine to control withdrawal; it is a retrospective review of seven infants ranging in age from 3 to 24 months. The patients had received a continuous fentanyl infusion supplemented with intermittent doses of midazolam for sedation during mechanical ventilation.

Another feasible route for simultaneously preventing tolerance and blunting withdrawal syndrome would be to follow strict protocols for sedative rotation, changing the sedation/analgesia molecule according to a prespecified protocol: no consistent literature is available in children in this regard, so far.

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## 15.1 Introduction

Cardiac surgery intensive care unit (CSICU) is typically dedicated to the pre- and postoperative care of patients who have been operated for heart diseases. Therefore, CSICUs are essentially postoperative ICUs in which the great majority of patients have a length of stay of less than 24 h. A second smaller cohort of cardiac surgery patients spend a longer time in the intensive care area. Those patients are usually the oldest, the frailest, those with the heaviest comorbidities, or those who experienced complications after surgery. Anyway, sedation has a huge impact, even if with different meanings, on all cardiac patients independently from their length of stay. Moreover, the quality of anesthesia during the operation and of sedation in the early postoperative period has a huge impact in maintaining the efficiency of cardiac institutions.

For several details, sedation of cardiac patients does not differ from that of other critically ill patients. The reader is referred to the other chapters of this book for more detailed information about sedative drugs, prolonged sedation strategies, analgesia, and delirium. Only the most typical problems regarding sedation of patients after cardiac surgery and the quotes from literature about sedation and delirium in CSICU are reviewed in this chapter.

Sedative drugs are analyzed by the point of view of the heart and circulation, considering the factors posing cardiac patients at higher risk of suffering their side effects.

Postoperative sedation of patients at short length of stay in the ICU is described as part of the fast-track cardiac model of care.

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Delirium and agitation are common complications after cardiac surgery and are some of the most important causes of prolonged sedation and protracted ICU stay of standard cardiac patients. Factors predisposing and precipitating such complications are outlined as well as the complex relationship among them, sedation, and anesthesia.

At last, the actual controversy on which drug is preferable for sedation in cardiac patients and which of them has the least potential to cause delirium is also analyzed.

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## **15.2 Sedative Drugs by the Point of View of the Heart and Circulation**

Sedation rather than therapy would have the meaning to accomplish the goal of maintaining the patient calm, comfortable, and cooperative, in spite of the various insults to which he is exposed during his stay in ICU. It has been generally acknowledged that sedation is useful only if, and at the minimum extent, it is really needed, otherwise it would be potentially harmful, putting the patient at risk of experiencing the side effects of sedatives [1].

The most common limiting side effects of sedative drugs, other than that of respiratory depression, are those affecting the heart and the circulation. The cardiac patient, along with the limited cardiac reserve, the already compromised cardiovascular compensating mechanisms, the high preload dependency, and the unfavorable ventricular-arterial coupling, would be highly vulnerable to those side effects. The complex relationship between the most common sedatives and hemodynamics has been addressed in Chap. 9.

Most sedative drugs have a direct negative inotropic effect. This is true for volatile anesthetics that cause dose-dependent depression of contractile function lowering the release of  $\text{Ca}^{++}$  from the sarcoplasmic reticulum [2]. Conversely, there is emerging evidence of the preconditioning properties of volatile agents and their effect in improving the outcome after cardiac surgery [3]. However, halogenates have been rarely used for prolonged sedation even in CSICUs. Main reasons for this are that open circuits of modern ventilators do not allow the application of conventional vaporizers and that ICUs are not usually provided with adequate scavenging systems. The development of new anesthetic conserving devices able to supply inhaled anesthetic in open circuits through the reflector technology has renewed the interest in introducing inhaled anesthetic in ICU [4]. Due to their aforementioned protective effect on the heart, postoperative application of halogenates could be particularly attractive in patients with coronary artery disease [5].

Even the majority of intravenous hypnotics have some effect on myocardial contraction. Thiopental has the most negative effect on inotropism, and etomidate has the least, while propofol and midazolam have a somewhat intermediate effect [6]. Conversely ketamine, despite a slight direct negative inotropic effect, has an overall positive cardiovascular profile, due to central sympathetic stimulation and inhibition of neuronal catecholamine uptake [7].

A common effect through which most hypnotics have an impact on hemodynamics of cardiac patients is also the vasodilation at the level of peripheral vascular muscular arteries. This is one of the effects by which volatile anesthetics (isoflurane, sevoflurane, desflurane) produce hypotension. Nevertheless, also propofol causes a profound dose-dependent drop of systemic vascular resistances. Therefore, the overall effect of propofol on patient's hemodynamics is hypotension that is proportionally worse if left ventricular dysfunction occurs [7]. The benzodiazepine midazolam has a less profound cardiovascular impact than propofol, affecting less both cardiac index and peripheral resistances. The potent  $\alpha_2$ -adrenergic agonist dexmedetomidine is gaining popularity for its adjuvant properties, to improve sedation and analgesia in cardiac patients, although the effect on patient hemodynamics is usually negative, through the decrease of cardiac output, systemic vascular resistances, and also heart rate.

The most used sedatives in the cardiac surgery setting are propofol, dexmedetomidine, and the short-acting benzodiazepine midazolam. Although midazolam has the shortest half-life among benzodiazepines, it could produce unpredictable prolonged sedation in patients with postoperative complications and reduced clearance. Conversely, the half-life of propofol is the shortest among the other intravenous hypnotics, and its duration is more predictable. For this reason, propofol is still the most commonly used drug for sedating patients even in CSICU in spite of its aforementioned side effects on hemodynamics [8].

In conclusion, whatever the drug used, the overall effect on hemodynamics is rather appreciable, usually dose dependent, and more pronounced in patients with the worst cardiovascular compromise [7]. Therefore, the need to sustain blood pressure with increasing dose of vasoactive drugs along with increasing depth of sedation is rather common and more appreciable for cardiac patients than for other critically ill patients.

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### **15.3 Sedative Strategy of Patients at Short Length of Stay in CSICU: The Fast-Track Cardiac Model**

The advances made by cardiac surgery and perfusion techniques in the last 20 years resulted in the readiness of the majority of cardiac surgery patients to be awakened and extubated in the early postoperative period. As a matter of course, anesthesia, sedation, and the overall postoperative management of cardiac surgery patients had to fulfill this criterion. Therefore, cardiac anesthesia gradually shifted from the traditional high-dose opiate technique, used in the past, to a more balanced modern approach, combining low or moderate dose of narcotics with short-acting anesthetics. Sedation and analgesia achieved with shorter-acting drugs such as propofol and lower dose of opiates or with the short-acting opiate remifentanyl was established also in the postoperative period, in order to initiate weaning from the ventilator as soon as the patient was ready for it.

This model is called fast track and is actually the most popular management strategy among CSICUs all over the world [9]. Nevertheless, the type of anesthesia

**Table 15.1** The fast-track cardiac model in use in Azienda Ospedaliera Careggi—Firenze

Operating room			
Premedication		Diazepam 0.05–0.2 mg/kg on the day of surgery	
Anesthesia induction		Fentanyl 0.5–3 µg/kg	
		Sufentanil 0.25–1 µg/kg	
		Midazolam 0.05–0.2 mg/kg	
		Propofol 0.5–2 mg/kg	
Muscle relaxation		Rocuronium 0.6–0.9 mg/kg (single dose at the induction)	
Anesthesia maintenance		Remifentanyl 0.1–0.3 µg/kg/min	
		Sufentanil 0.3–1 µg/kg/h titrated until the end of CPB	
		Propofol 1–3 mg/kg/h	
		Sevoflurane 0.5–1.5 MAC	
		Desflurane 0.5–1.5 MAC	
		Preservation of normothermia at the end of surgery	
Surgery		Maintenance of normothermia or mild hypothermia during CPB	
		Off-pump procedures when possible	
		Minimally invasive procedures when indicated	
		Minimize bleeding (thromboelastography-guided therapy)	
Intensive care unit			
Sedation	Hypnotic	Propofol	0.5–1 mg/kg/h (stop at weaning)
Analgesia	Opioids	Remifentanyl	0.05–0.1 µg/kg/min (stop at weaning)
		Morphine	1–3 mg before starting weaning and if VAS >3
		Acetaminophen	0.5–1 g before starting weaning and then Q8h
		Ketorolac	30 mg as rescue analgesic if VAS still >3
Active rewarming: until 37 °C core temperature is regained			
Weaning started as soon as		Core temperature > 36.9 °C	
		Stable hemodynamics	
		No significant ECG abnormalities	
		No excessive bleeding (≤100 ml/h)	
Extubation as soon as		Conscious and obeyed commands	
		Spontaneous ventilation with pressure support of 10–12 cmH <sub>2</sub> O	
		Positive end-expiratory pressure (PEEP) of 5 cmH <sub>2</sub> O	
		Fraction of inspired oxygen (FiO <sub>2</sub> ) of ≤0.4	

during surgery, and of sedation in ICU, although pivotal, is only part of the overall cardiac patient management, leading to the early weaning of patients from the ventilator.

The main reason of success of the fast-track model of care is merely organizational, due to the increasing demand of cardiac surgery care, unbalanced by limited resources. Furthermore, huge factors are also the belief that excessive or prolonged sedation could favor the insurgence of delirium and prolong the patient's ICU stay and the need for circulatory support, thus increasing the total cost of care and worsening outcomes [10]. Although this could be true, several trials and meta-analysis failed to find an ultimate outcome advantage of this model of care in comparison with the standard one [11]. A recent Cochrane review concluded that the fast-track

model has risks of mortality and major postoperative complications similar to those of conventional care but appear to be safe in patients at low or moderate risk [12]. Anyway, while the time to extubation, the length of the intensive care treatment, and sometimes also the patient length of stay in ICU are reduced, the total length of stay in the hospital is generally unchanged [13].

A method for maximizing the advantage of the fast-track model would be that of developing an institutional structure comprising a dedicated cardiac surgery PACU. When applied on selected patients at lower risk (EuroSCORE less or equivalent to 10, not hemodialysis dependent, and not in cardiogenic shock), patients could be early extubated in the dedicated PACU, and safely discharged in the step-down care unit in the same day of surgery, without passing through the CSICU [14]. These authors found a shortened length of stay of the early extubated patients in the intensive care area but failed to prove any differences in the total hospital length of stay in respect to patients submitted to standard care inside a CSICU. Advanced age and left ventricular dysfunction were the main preoperative predictors of failure of a similar sedation protocol [15].

However, the ability to perform a goal-directed sedation and analgesia is unquestionable advantage of this model of care, that is, to tailor sedation, anxiolysis, and analgesia to every individual patient's need, both in those who achieve early readiness to be weaned and in the frailest or hemodynamically instable patients who do not. Actually, short-acting sedatives are crucial also for those patients who cannot be extubated in a short time or in whom early or repetitive neurological windows are needed, as are patients at higher risk of neurologic complication after complex cardiac or aortic surgery. Our institutional cardiac fast-track model is summarized in Table 15.1.

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## 15.4 Delirium in CSICU

Delirium is a common complication after cardiac surgery. Its incidence is highly variable among the various studies that have been set in CSICU, from 3.07% [16] to 52% [17]. Reasons for this variability may be the different case mix, the specific tool used to make the diagnosis, and the difficulty to recognize some types of delirium, especially the hypoactive form [18]. Although delirium is often a self-limiting occurrence, it is one of the main reasons why cardiac patients may lengthen their stay in ICU slowing down the weaning from mechanical ventilation [19]. Moreover, delirium has been associated with persistent cognitive dysfunction, reduced quality of life, and even higher mortality [20].

Predisposing factors, frequently associated with cardiac surgery, which put this specialty at higher risk of developing delirium are the advanced age of cardiac patients and the coexisting morbidities as cerebrovascular disease, cognitive impairment, peripheral vascular disease, atrial fibrillation, depression, or previous history of stroke [10]. On the other hand, precipitating factors for developing postoperative delirium are prolonged duration of sedation and mechanical ventilation, prolonged duration of surgery or aortic cross-clamping, anemia, and blood transfusion [10].

Also hypokalemia and SOFA score has been highly correlated with delirium, as well as sepsis, hyponatremia, cardiogenic shock, low left ventricular ejection fraction (<30%), uncontrolled diabetes mellitus, history of seizures, and the high total number of medications [21].

The type of surgery also seems to play a huge role, being valve surgery or combined, valve and coronary artery bypass graft surgery, at higher risk for postoperative delirium than coronary surgery alone [22]. Similarly, this complication is more common when extra corporeal circulation is needed if compared with off-pump surgery. Nevertheless, delirium is particularly common after operation for which circulatory arrest is needed. In a recent survey of 100 patients operated for Type A aortic dissection, 34% had postoperative delirium, and this was independently found to be associated with cerebrovascular disease history, CPB duration, intubation time, hypoxia, and most of all with length of surgery, with an OR (95% CI) of 3.21 (1.43–5.72) and  $p = 0.002$  [23].

Even the way of delivering anesthesia and sedation could be of importance. The depth of hypnosis during anesthesia has been directly correlated with postoperative delirium in other settings [24]. Fentanyl is an opiate commonly used intraoperatively that could play a role in the insurgence of delirium. Burkhart [25] found a 3.4 (95% CI 1.41–8.14,  $p = 0.006$ ) times higher likelihood of developing delirium, for every 10  $\mu\text{g/kg}$  increase in fentanyl dose used for anesthesia in cardiac surgery with CPB. These findings were even more striking when adjusted for the duration of surgery, where the odds ratio increased to 4.9 (95% CI 1.72–13.8,  $p = 0.003$ ) [25]. The use of benzodiazepines as a precipitating factor in predisposed patients is debated [26]. Also, the role of the dissociative anesthetic ketamine for delirium insurgence in cardiac surgery is controversial. Even if hallucinations and delirium are well-known adverse effects of this drug, unexpectedly, Hudetz [27] found that a single subanesthetic dose of ketamine (0.5 mg/kg) at the induction of anesthesia attenuated postoperative delirium. Conversely, even in CSICU, the centrally acting  $\alpha$ -2-adrenergic agonist, dexmedetomidine, has been found to prevent postoperative delirium [28]. Preoperative use of antipsychotics, within the year before surgery, has been found to worsen 1.57 times (OR = 1.57, 95% CI 1.26–1.95;  $p < 0.001$ ) the risk of developing delirium after surgery [29]. In the same study also, antidepressants (OR = 2.01, 95% CI 1.75–2.25;  $p < 0.001$ ), anticholinergic drugs (OR = 3.99; 95% CI 2.26–7.05;  $p < 0.001$ ), and benzodiazepines (OR = 1.40; 95% CI 1.28–1.53;  $p < 0.001$ ) were variably correlated with delirium. There are also several other drugs frequently used in cardiac patients for which a correlation with postoperative delirium has been considered. The role of statins has been proposed, particularly in non-cardiac surgery [29]. Norkiene et al. [16] found that inotropes, if infused for more than 12 h after cardiac surgery, increased the risk of postoperative delirium (OR = 8.04, 95% CI 1.1–60.6;  $p = 0.002$ ). Preoperative  $\beta$ -blockers were also found to be associated with a significantly lower prevalence of hypoactive delirium [18], even if literature shows conflicting results, and other authors found  $\beta$ -blockers to increase the odds of delirium by 1.9 times [26]. On the other hand, the indication for each drug could act as a confounding factor, and has also to be considered, while searching for a correlation between delirium and a specific drug. Namely,

**Table 15.2** Factors predisposing and precipitating delirium in CSICU

1. Predisposing factors	Precipitating factors
Advanced age	Duration and depth of sedation
Cerebrovascular disease	Duration of mechanical ventilation
Preexisting cognitive impairment	Duration of surgery
Peripheral vascular disease	Duration of aortic cross-clamping
Previous atrial fibrillation	Anemia
Depression	Blood transfusion
History of stroke	Type of surgery
Uncontrolled diabetes mellitus	Type and depth of anesthesia and sedation
Sepsis	Hypokalemia
Cardiogenic shock	Hyponatremia
Ejection fraction <30%	Fentanyl dose
History of seizures	Inotropes
Preoperative drugs	

preoperative depression or psychosis may play a role in provoking delirium instead of antidepressants or antipsychotics, as well as a preexisting cerebrovascular disease or an ongoing low cardiac output syndrome may act as the trigger, rather than statins or inotropes.

In conclusion, the “3-Strike” paradigm for delirium, recently proposed by Arora et al. [30] in cardiac patients, arranges the aforementioned risk factors, starting from those that affect the basal vulnerability of the brain of older patients, on which the surgical insult superimposes as a cardiac stressor, and postoperative factors like hemodynamic perturbations, drugs, sedation, and environmental factors could definitely act as the final trigger for delirium occurrence.

Although many of the predisposing and precipitating factors listed above are not modifiable (Table 15.2), early individuation of patients at higher risk for developing delirium and the optimization of the few modifiable aspects are pivotal in the management of this challenging postoperative complication [31].

Choosing the sedative, and most of all the correct sedation strategy in the postoperative period, as the fast-track weaning protocol, and most of all maintaining the minimum sedation needed for the minimum time [10], together with optimization of the environment, may be pivotal in preventing delirium [32]. Prophylactic melatonin administration (4 mg PO for 14 days or until ICU discharge) reduced the incidence of delirium from 20.8% to 8.4% in a prospective clinical observational study designed in a CSICU [33], while one single dose of sublingual administration of the second-generation antipsychotic risperidone (1 mg at the awakening in CSICU) reduced the incidence of delirium from 31.7% to 11.1% ( $p = 0.009$ ) in a randomized, double-blind, placebo controlled study [34]. Nonetheless, current guidelines do not suggest any drug for prevention of delirium in the ICU [31, 32].

Treatment of delirium in CSICU is supportive, involving close observation of patients, and sedatives (propofol) or antipsychotics (haloperidol, risperidone) are often required. Even morphine has been proposed as a reasonable alternative to haloperidol in the hyperactive form of delirium [35], as well as the serotonin 5HT-3 antagonist ondansetron (8 mg IV) which resulted as efficient as haloperidol but with less adverse effects [36]. Early administration of risperidone (0.5 mg orally BID

starting 4 h after extubation) has also been proposed [37] as well as postoperative dexmedetomidine when prolonged sedation is needed. Recently, a double-blind, placebo controlled trial of 4494 patients undergoing cardiac surgery with cardiopulmonary bypass found that dexamethasone (1 mg/kg IV after induction of anesthesia and before CPB) was associated with reductions in postoperative delirium [38]. Conversely, the effectiveness of the cholinesterase inhibitor rivastigmine (1.5 mg orally TID starting the evening before surgery to POD 6) in preventing delirium is still inconclusive and requires further investigation [39]. Despite negative recommendation in the latest American guidelines for sedation, analgesia, and delirium [32], haloperidol (0.03–0.15 mg/kg q 0.5–6 h or 0.04–0.15 mg/kg/h infusion) is still the first-line agent used worldwide for the treatment of delirium in CSICU [40]. Of note, it can be associated with extrapyramidal symptoms, malignant neuroleptic syndrome, and dose-dependent prolonged QT interval that is a risk factor for torsades de pointes, particularly in cardiac patients [41].

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## 15.5 Choosing the Sedative in CSICU: Which Drug Is Preferable?

The choice of the sedative agent is highly different among countries and centers, thus suggesting that this is determined more by local preference than by evidence-based practice.

Propofol [40] (0.3–4.8 mg/kg/h) is the most used sedative drug in CSICU, but due to the aforementioned cardiovascular effects, it may cause clinically significant hypotension in patients who have unstable hemodynamics. Furthermore, propofol may also cause respiratory depression, and both effects can be amplified by opioids.

Dexmedetomidine [40] (0.2–1.4 µg/kg/h infusion) is a highly specific  $\alpha_2$ -adrenoreceptor agonist approved for ICU sedation both in Europe and the USA. Unlike propofol, at clinically effective doses, continuous sedation with intravenous dexmedetomidine does not interfere with the normal course of ventilator weaning and extubation because it does not depress respiratory drive, while lowering blood pressure and causing bradycardia, as a consequence of its sympatholytic effects. It has both analgesic and anxiolytic effects, and it is gaining popularity because of its presumed effect of preventing delirium also in the cardiac surgery setting, where Djaiani [42] found in a large prospective randomized clinical trial an absolute risk reduction for postoperative delirium of 14%, suggesting that dexmedetomidine-based sedation strategy prevents 1 case of delirium for every 8 patients. By the way, a recent Cochrane review [43] concluded that there was no clear evidence supporting dexmedetomidine in reducing the risk of delirium, and the quality of evidence ranged from very low to low. Most of all, dexmedetomidine produces at least light sedation and is not applicable in any case as a substitute for the other commonly used sedatives such as propofol or benzodiazepines when a deeper state of sedation is needed [44]. Nevertheless, the potential of this drug to prevent postoperative delirium could be linked more to the lighter sedation



produced, than to direct effect of the drug. In this light, we could interpret the result of a paper from Chorney [44], in which the protective effect of dexmedetomidine was not evident if compared with no sedation at all.

Benzodiazepines [40], midazolam (0.02–0.08 mg/kg iv q 0.5–2 h bolus or 0.04–0.2 mg/kg/h infusion), and lorazepam (0.02–0.06 mg/kg iv q 2–6 h bolus or 0.01–0.1 mg/kg/h infusion) are less used for sedation in CSICU because of their tendency to accumulate, especially when prolonged infusion is needed, carrying the risk of oversedation and unpredictable recovery [8].

Typically, as in other settings, sedation and anxiolysis must be properly combined with analgesia, and for this purpose, intravenous opiates combined with non-steroidal anti-inflammatory medications are often used and tailored on the patient's need by means of analogic, visual, or behavioral scales (see Chap. 2).

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### Conclusions

Sedation has a pivotal role in CSICU. Proper sedation, as part of the fast-track cardiac model of care, allows earlier awakening, weaning, and extubation of patients after heart operations. These patients, due to their limited cardiac reserve, are more prone to the adverse cardiovascular effects of sedatives. Therefore, the optimal sedation for them is the least sedation possible for the minimum time, according with their needs. Delirium is a common but dreadful complication after cardiac surgery. Cardiac patients are particularly at risk to develop postoperative delirium for their intrinsic features, and delirium itself could prolong their time to recovery and their length of stay in the hospital and even increase their risk of death. A too deep or unnecessarily prolonged sedation could favor the occurrence of delirium and postoperative cognitive dysfunction. On the other hand, the occurrence of delirium itself demands to sedate patients again. In some cases, a deep sedation is needed, and this can initiate and precipitate a harmful vicious circle. Although many sedatives and drugs are available, none of them have a clear favorable result, and none of them are devoid of side effects. Some recent literature seems to point out a presumed helpful influence of dexmedetomidine, but the quality of evidence is low. Further studies are still needed to address the best drug and the best strategy to manage sedation inside the CSICUs as to minimize the well-recognized unfavorable effects of sedatives on cardiac patients.

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